L9 ANSWER 1 OF 8 USPATFULL
AB The present invention involves the novel use of various classes of drugs, such as H.sub.2 and H.sub.3 agonists, as erectogenic agents in the treatment of male and female sexual dysfunction.
AN 1999:110350 USPATFULL
TI Compositions
IN Dias Nahoum, Cesar Roberto, P.O. Box 1539, King of Prussia, PA, United States 19406-0939
PI US 5952361 19990914 <--
AI US 1998-37097 19980309 (9)
RLI Division of Ser. No. US 1995-444130, filed on 18 May 1995, now patented,
Pat. No. US 5773457 which is a continuation of Ser. No. US 1995-381945, filed on 15 Feb 1995
PRAI BR 1992-3277 19920821
DT Utility
FS Granted
EXNAM Primary Examiner: Reamer, James H.
LREP Dinner, Dara L., Venetianer, Stephen, Kinzig, Charles M.
CLMN Number of Claims: 34
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5952361 19990914 <--
SUMM The use of **galanthamine** for treatment of physiologic and psychogenic mediated male erectile impotence is disclosed in U.S. Pat. No. 5,177,070 and U.S. Pat.. . .
SUMM . . . which may be anionic, cationic or zwitterionic, in particular lecithins, such as soya bean lecithins, egg lecithin or egg phosphatide,
cholesterol or long-chain fatty acids such as oleic acid;

L9 ANSWER 2 OF 8 USPATFULL
AB The present invention involves the novel use of H.sub.2 and H.sub.3 agonists, as erectogenic agents in the treatment of male and female sexual dysfunction in an animal, including humans. The H.sub.2 and H.sub.3 agonists may be administered by intracavernousm injection, topically, transdermally, or intraurethrally. The method of use may also
include a second therapeutic agent which either facilitates, potentiates
or is erectogenic. The second agent may be administered sequentially or contemporaneously with either the H.sub.2 or H.sub.3 agonist.
AN 1999:63326 USPATFULL
TI Compositions
IN Nahoum, Cesar Roberto Dias, SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220 P.O. Box 1539, King of Prussia, PA, United
States 19406-0939
PA Nahoum, Cesar Roberto Dias, Rio de Janeiro, Brazil (non-U.S. individual)
PI US 5908853 19990601 <--
WO 9404120 19940303 <--
AI US 1995-381945 19950215 (8)
WO 1993-BR27 19930818
19950215 PCT 371 date
19950215 PCT 102(e) date
PRAI BR 1992-3277 19920821
DT Utility

FS Granted
EXNAM Primary Examiner: Harrison, Robert H.
LREP Dinner, Dara L., Venetianer, Stephen
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1523
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5908853 19990601 <--
WO 9404120 19940303 <--
DETD The use of **galanthamine** for treatment of physiologic and psychogenic mediated male erectile impotence is disclosed in U.S. Pat. No. 5,177,070 and U.S. Pat.. . .
DETD . . . which may be anionic, cationic or zwitterionic, in particular lecithins, such as soya bean lecithins, egg lecithin or egg phosphatide,
cholesterol or long-chain fatty acids such as oleic acid;

L9 ANSWER 3 OF 8 USPATFULL
AB The present invention involves the novel use of various classes of drugs, such as H.sub.2 and H.sub.3 agonists, as erectogenic agents in the treatment of male and female sexual dysfunction.
AN 1998:75603 USPATFULL
TI Compositions
IN Nahoum, Cesar Roberto Dias, SmithKline Beechman Corporation Corporate Intellectual Property, UW2220 P.O. Box 1539, King of Prussia, PA, United States 19406-0939
PA Nahoum, Cesar Roberto Dias, Rio de Janeiro, Brazil (non-U.S. individual)
PI US 5773457 19980630 <--
AI US 1995-444130 19950518 (8)
RLI Continuation of Ser. No. US 1995-381945, filed on 15 Feb 1995
DT Utility
FS Granted
EXNAM Primary Examiner: Reamer, James H.
LREP Dinner, Dara L., Venetianer, Stephen, Lentz, Edward T.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1454
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5773457 19980630 <--
DETD The use of **galanthamine** for treatment of physiologic and psychogenic mediated male erectile impotence is disclosed in U.S. Pat. Nos. 5,177,070 and 4,663,318.
DETD . . . which may be anionic, cationic or zwitterionic, in particular lecithins, such as soya bean lecithins, egg lecithin or egg phosphatide,
cholesterol or long-chain fatty acids such as oleic acid;

L9 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB Hepatopathy was induced in 18 goats by single intravenous (i/v) injection of paracetamol @ 400 mg/kg body weight. The therapeutic efficacy of a herbal preparation (containing equal parts of Berberis aristata, Solanum nigrum and Achyranthes aspera) was studied. It was given orally @ 1 g/kg body weight for 10 days in 12 goats. The remaining 6 goats served as untreated control. Haematological, blood biochemical and dye (Bromosulphalcin) retention studies were carried out at different intervals. Histopathological studies of liver were done at the end of 20

days of experiment. There was an increase in total leukocyte count (TLC), serum **cholesterol**, blood urea nitrogen (BUN), total lipids, triglycerides, bilirubin, globulin, bromosulphalcin (BSP) per cent retention, activities of alanine aminotransferase (ALT), asparate aminotransferase (AST) and gamma glutamyl transferase (GGT) and a decrease in haemoglobin (IIb), packed-cell volume (PCV), total erythrocyte count (TEC), total protein and albumin: globulin (A:G) ratio. Histopathologically liver showed characteristic lesions of hepatotoxicity. The drug preparation was effective in curing these cases as evidenced from the reversal of all the pathological changes towards normalcy following treatment.

AN 1993:392643 BIOSIS
DN PREV199396067943
TI Effect of an herbal preparation in experimentally induced hepatopathy in goats.
AU Sharma, M. C.; Dixit, S. K.; Lal, S. B.; Bhaumik, Anup; Baig, J.
CS Div. Experimental Med. Surg., Indian Veterinary Res. Inst., Izatnagar, Uttar Pradesh 243 122 India
SO Indian Journal of Animal Sciences, (1993) Vol. 63, No. 6, pp. 606-610. ISSN: 0367-8318.
DT Article
LA English
SO Indian Journal of Animal Sciences, (1993) Vol. 63, No. 6, pp. 606-610. ISSN: 0367-8318.
AB. . . were done at the end of 20 days of experiment. There was an increase in total leukocyte count (TLC), serum **cholesterol**, blood urea nitrogen (BUN), total lipids, triglycerides, bilirubin, globulin, bromosulphalcin (BSP) per cent retention, activities of alanine aminotransferase (ALT), asparate. . .
IT Miscellaneous Descriptors
ANTIULCER-DRUG; **GALANTHAMINE** HYDROBROMIDE; GASTRIC TISSUE; GASTRIC ULCER; LIPID PEROXIDATION; METAMISYL; METHACIN; PROSERINUM

L9 ANSWER 5 OF 8 MEDLINE
AN 73229218 MEDLINE
DN 73229218 PubMed ID: 5162382
TI [Influence of an anticholinesterase substance, Nivalin, on the development of experimental arteriosclerosis].
Etude de l'influence de la substance anticholinesterasique-Nivaline-sur le developpement de l'atherosclerose experimentale.
AU Michailov M; Zlateva M; Dimitrov P; Zografski B
SO COR ET VASA, **(1971)** 13 (4) 291-5.
Journal code: 0372614. ISSN: 0010-8650.
CY Czechoslovakia
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 197310
ED Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19731009
SO COR ET VASA, **(1971)** 13 (4) 291-5.
Journal code: 0372614. ISSN: 0010-8650.
CT Check Tags: Animal

Arteriosclerosis: DT, drug therapy
*Arteriosclerosis: ME, metabolism
Cholesterol, Dietary
Cholinesterase Inhibitors: AD, administration & dosage
*Cholinesterase Inhibitors: ME, metabolism
Cholinesterase Inhibitors: TU, therapeutic use
Diet, Atherogenic
Disease Models, Animal
Galanthamine: AD, administration & dosage
***Galanthamine: ME, metabolism**
Galanthamine: TU, therapeutic use
Models, Biological
Rabbits
RN **357-70-0 (Galanthamine)**
CN 0 (**Cholesterol**, Dietary); 0 (Cholinesterase Inhibitors)

L9 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS
AB Rats subjected to exhausting swimming exercises on a mountain top (3200 m)
showed much less endurance than did rats at sea level, and also showed loss of liver, heart, and skeletal muscle glycogen [9005-79-2], increased serum free fatty acids, decreased plasma phospholipids, increased heart **cholesterol** [57-88-5], and decreased adrenal gland wt. and adrenal ascorbic acid [50-81-7]. The monoamine oxidase inhibitor iprazide (I) [54-92-2] at 2 mg/kg orally daily for 6 days did not affect swimming time by the animals, but decreased plasma **cholesterol** and increased plasma phospholipids in animals subjected to swimming at low altitudes and
not those at high altitudes. The cholinesterase inhibitor **galanthamine** [**357-70-0**] at 0.3 mg/kg/day s.c. for 6 days increased swimming time and decreased **cholesterol** and free fatty acids in the plasma. Neither of these drugs affected carbohydrate metab or the state of the adrenal glands in the animals.
AN 1973:119732 CAPLUS
DN 78:119732
TI Effect of exhausting emotional-muscular loads on some metabolic indexes in
rats under normal and lowered barometric pressure conditions affected by the action of iprazide and **galanthamine**
AU Kopytin, B. M.; Rodina, V. S.; Dzhumaliev, A. D.; Kinzburskii, Ya. N.; Bakina, E. E.; Sokorenko, O. I.
CS Kirg. Gos. Med. Inst., Frunze, USSR
SO Trudy Kirgizskogo Gosudarstvennogo Meditsinskogo Instituta (**1971**), 69, 46-53
CODEN: TKRMAS; ISSN: 0371-8778
DT Journal
LA Russian
TI Effect of exhausting emotional-muscular loads on some metabolic indexes in
rats under normal and lowered barometric pressure conditions affected by the action of iprazide and **galanthamine**
SO Trudy Kirgizskogo Gosudarstvennogo Meditsinskogo Instituta (**1971**), 69, 46-53
CODEN: TKRMAS; ISSN: 0371-8778
AB Rats subjected to exhausting swimming exercises on a mountain top (3200 m)
showed much less endurance than did rats at sea level, and also showed loss of liver, heart, and skeletal muscle glycogen [9005-79-2], increased serum free fatty acids, decreased plasma phospholipids, increased heart **cholesterol** [57-88-5], and decreased adrenal gland wt. and adrenal

ascorbic acid [50-81-7]. The monoamine oxidase inhibitor iprazide (I) [54-92-2] at 2 mg/kg orally daily for 6 days did not affect swimming time by the animals, but decreased plasma **cholesterol** and increased plasma phospholipids in animals subjected to swimming at low altitudes and not those at high altitudes. The cholinesterase inhibitor **galanthamine** [**357-70-0**] at 0.3 mg/kg/day s.c. for 6 days increased swimming time and decreased **cholesterol** and free fatty acids in the plasma. Neither of these drugs affected carbohydrate metab or the state of the adrenal glands in the animals.

IT Heart, composition
(**cholesterol** and glycogen of, in fatigue at high altitude)

IT Atmosphere, environmental
(high altitude, iprazide and **galanthamine** effect on metabolism in, in fatigue)

IT Fatigue, biological
(metabolism in, iprazide and **galanthamine** effect on, at high altitude)

IT Lipids, composition
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, iprazide and **galanthamine** effect on, in fatigue at high altitude)

IT 54-92-2 **357-70-0**
RL: PRP (Properties)
(metabolism response to, in fatigue at high altitude)

IT 57-88-5, biological studies
RL: BIOL (Biological study)
(of blood plasma and heart, iprazide and **galanthamine** effect on, in fatigue at high altitude)

L9 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1

AB cf. preceding abstr. Rabbits (24) divided into 2 groups of 18 and 6 animals were (a) given 0.5 mg. nivalin (I)/day for 30 days intramuscularly, and inoculated intraperitoneally at the start of I treatment and 10, 15, and 20 days later with 0.5, 1, 3, and 5 ml. of a vaccine active against Salmonella typhimurium (a suspension of S. typhimurium (agar-broth cultures) in 0.5% HCHO in physiol. soln. kept 6 hrs. at 37.degree. and then stored at 4-5.degree.), and (b) vaccinated as above but without I (controls). Detns. of antibody titer and **cholesterol** (II) level, and microelectrophoretic pattern were performed on blood withdrawn by cardiac puncture. Antibody titer was 1:200-1:400 in I-treated animals and 1:50-1:100 in controls, with an antibody av. rate of 355 for the I-treated against 58.3 for controls. A redn. in albumin fraction and an increase in .gamma.-globulin with an inversion of the albumin-to-globulin ratio were the most significant changes for the 2 groups, the most significant difference being a more marked rise in .gamma.-globulin for I-treated animals. II blood level (basals) was 55-99 (av. 68.2) for the I-treated and 55-75 (av. 63.5 mg.%) for controls, and after treatment was 29-75 (av. 54.3) for the I-treated compared to 8-25 (av. 16.1 mg.%) for controls.

AN 1966:22259 CAPLUS

DN 64:22259

OREF 64:4132a-c

TI Nivalin. II. Action of nivalin on specific immunologic factors

AU Lombardo, G.; Arena, G.; Londrillo, A.

CS Univ. Messina, Italy

SO Minerva Pediatrica (**1963**), 15(47), 1353-7
CODEN: MIPEA5; ISSN: 0026-4946

DT Journal

LA Italian
SO Minerva Pediatrica (**1963**), 15(47), 1353-7
CODEN: MIPEA5; ISSN: 0026-4946
AB cf. preceding abstr. Rabbits (24) divided into 2 groups of 18 and 6 animals were (a) given 0.5 mg. nivalin (I)/day for 30 days intramuscularly, and inoculated intraperitoneally at the start of I treatment and 10, 15, and 20 days later with 0.5, 1, 3, and 5 ml. of a vaccine active against Salmonella typhimurium (a suspension of S. typhimurium (agar-broth cultures) in 0.5% HCHO in physiol. soln. kept 6 hrs. at 37.degree. and then stored at 4-5.degree.), and (b) vaccinated as above but without I (controls). Detns. of antibody titer and **cholesterol** (II) level, and microelectrophoretic pattern were performed on blood withdrawn by cardiac puncture. Antibody titer was 1:200-1:400 in I-treated animals and 1:50-1:100 in controls, with an antibody av. rate of 355 for the I-treated against 58.3 for controls. A redn. in albumin fraction and an increase in .gamma.-globulin with an inversion of the albumin-to-globulin ratio were the most significant changes for the 2 groups, the most significant difference being a more marked rise in .gamma.-globulin for I-treated animals. II blood level (basals) was 55-99 (av. 68.2) for the I-treated and 55-75 (av. 63.5 mg.%) for controls, and after treatment was 29-75 (av. 54.3) for the I-treated compared to 8-25 (av. 16.1 mg.%) for controls.
IT 1953-04-4, **Galanthamine**, hydrobromide
(antibodies, **cholesterol** and proteins in blood after treatment with)
IT 57-88-5, **Cholesterol**
(in blood, nivalin effect on)

L9 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
AB A review of the pharmacol. and clin. properties of **galanthamine** -HBr (nivalin, I) is presented. The influence of I on lysozyme activity, complement activity, spontaneous hemolytic, and natural hemolytic activity was studied. I was given intramuscularly at 0.5 mg./day for 30 days to 20 rabbits, and 6 other animals (controls) were given 0.5 ml./day of physiol. soln. for the same period. Blood was withdrawn by cardiac puncture before treatment, and 15 and 30 days after the start, and lysozyme activity, complement activity, and spontaneous and natural hemolytic activity were detd. Lysozyme activity was 4.5 (2-8) for the 1st group, and 4 (2-8) for the 2nd group (controls) at basal conditions, and was 172.8 (32-512) and 568.8 (512-1024) units after, 15 and 30 days of I treatment, resp., compared with no change for controls. Complement activity was 1-2.5 (1st), and 1.5-2.5 (2nd group) at basal conditions, and was 2.5-4.5, and .gtoreq.5 in most cases after 15 and 30 days, resp., of I treatment compared with no changes for controls. Spontaneous and natural hemolytic activity did not change appreciably in comparison with basal activity after 15 and 30 days of treatment. 34 references.
AN 1966:22258 CAPLUS
DN 64:22258
OREF 64:4131g-h,4132a
TI Nivalin. I. Action of nivalin on nonspecific immunologic factors
AU Lombardo, G.; Arena, G.; Londrillo, A.
CS Univ. Messina, Italy
SO Minerva Pediatrica (**1963**), 15(47), 1350-3
CODEN: MIPEA5; ISSN: 0026-4946
DT Journal
LA Italian

SO Minerva Pediatrica (**1963**), 15(47), 1350-3
CODEN: MIPEA5; ISSN: 0026-4946
AB A review of the pharmacol. and clin. properties of **galanthamine** -HBr (nivalin, I) is presented. The influence of I on lysozyme activity, complement activity, spontaneous hemolytic, and natural hemolytic activity was studied. I was given intramuscularly at 0.5 mg./day for 30 days to 20 rabbits, and 6 other animals (controls) were given 0.5 ml./day of physiol. soln. for the same period. Blood was withdrawn by cardiac puncture before treatment, and 15 and 30 days after the start, and lysozyme activity, complement activity, and spontaneous and natural hemolytic activity were detd. Lysozyme activity was 4.5 (2-8) for the 1st group, and 4 (2-8) for the 2nd group (controls) at basal conditions, and was 172.8 (32-512) and 568.8 (512-1024) units after, 15 and 30 days of I treatment, resp., compared with no change for controls. Complement activity was 1-2.5 (1st), and 1.5-2.5 (2nd group) at basal conditions, and was 2.5-4.5, and .gtoreq.5 in most cases after 15 and 30 days, resp., of I treatment compared with no changes for controls. Spontaneous and natural hemolytic activity did not change appreciably in comparison with basal activity after 15 and 30 days of treatment. 34 references.
IT 1953-04-4, **Galanthamine**, hydrobromide
(antibodies, **cholesterol** and proteins in blood after treatment with)
IT 1953-04-4, **Galanthamine**, hydrobromide
(effect on complement and lysozyme activity in blood)

=> d hist

(FILE 'HOME' ENTERED AT 19:56:48 ON 17 JUN 2003)

FILE 'REGISTRY' ENTERED AT 19:56:55 ON 17 JUN 2003
L1 360 S GALANTHAMINE
L2 1 S GALANTHAMINE/CN
L3 43 S LYCORAMINE
L4 1 S LYCORAMINE/CN

FILE 'USPATFULL, CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 20:01:29 ON 17 JUN 2003
L5 2237 S GALANTHAMINE OR LYCORAMINE OR 21133-52-8/RN OR 357-70-0/RN
L6 527104 S CHOLESTEROL
L7 15 S L5 AND L6
L8 9 S L7 AND PY<2002
L9 8 DUP REM L8 (1 DUPLICATE REMOVED)

=> s attention or cognitive or cognition or memory
3 FILES SEARCHED...
L10 1421333 ATTENTION OR COGNITIVE OR COGNITION OR MEMORY

=> s l5 and l10
L11 317 L5 AND L10

=> s lipid or hyperlipidemia or dyslipidemia or hypolipidemic or lipoprotein or cholesterol
L12 1444847 LIPID OR HYPERLIPIDEMIA OR DYSLIPIDEMIA OR HYPOLIPIDEMIC OR LIPOPROTEIN OR CHOLESTEROL

```
=> s l11 and l12
L13         16 L11 AND L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14         16 DUP REM L13 (0 DUPLICATES REMOVED)

=> s l14 and py<2002
   4 FILES SEARCHED...
L15          6 L14 AND PY<2002

=> d l15 1-6 ab bib kwic

L15  ANSWER 1 OF 6  USPATFULL
AB      The invention related to a GPI-anchored p97 and a soluble form of p97
        and derivatives thereof and methods for preparing the same. Methods of
        using p97 in modulating iron transport, in the delivery of therapeutic
        agents, and in the treatment of conditions involving disturbances in
        iron metabolism are described. The treatment and diagnosis of
        Alzheimer's Disease in view of the finding that p97 and transferrin
        receptor are markers for microglial cells associated with senile
plaques
        are also described.
AN      1999:141601  USPATFULL
TI      Use of p97 and iron binding proteins as diagnostic and therapeutic
        agents
IN      Jefferies, Wilfred A., South Surrey, Canada
        McGeer, Patrick L., Vancouver, Canada
        Rothenberger, Sylvia, Epalinges, Switzerland
        Food, Michael R., Vancouver, Canada
        Yamada, Tatsuo, Tokyo, Japan
        Kennard, Malcolm, Vancouver, Canada
PA      University of British Columbia, Vancouver, Canada (non-U.S.
corporation)
PI      US 5981194              19991109                                <--
AI      US 1995-520933          19950831 (8)
RLI     Continuation-in-part of Ser. No. US 367224
DT      Utility
FS      Granted
EXNAM   Primary Examiner: Feisee, Lila; Assistant Examiner: Davis, Minh-Tam
LREP    Bereskin & Parr
CLMN    Number of Claims: 10
ECL     Exemplary Claim: 1
DRWN    83 Drawing Figure(s); 64 Drawing Page(s)
LN.CNT 5517
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI      US 5981194              19991109                                <--
SUMM    . . . Within the context of the DSM-IIIR criteria, dementia is
        understood to involve "a multifaceted loss of intellectual abilities,
        such as memory, judgement, abstract thought, and other higher
        cortical functions, and changes in personality and behaviour."
(DSM-IIR,
        1987).
SUMM    . . . as the Mini-Mental test (Foldstein et al., J. Psych. Res.
        12:189-198, 1975); (b) deficits in two or more areas of
        cognition; (c) progressive worsening of memory and
        other cognitive functions; (d) no disturbance of
        consciousness; (e) onset between ages 40 and 90, most often after age
        65; and (f). . .
SUMM    . . . are believed to be the sites of damage in the earliest stages
```

of Alzheimer's Disease's. Therefore, patients may exhibit significant **memory** loss, and yet exhibit no abnormalities in cerebral blood flow or metabolism.

SUMM . . . Huperzine A and B: Two Selective AChE Inhibitors," Current Research in Alzheimer's Therapy, Giacobini and Becker (eds.), pp. 289-393, 1988); **galanthamine** (Domino, "**Galanthamine**: Another Look at an Old Cholinesterase Inhibitor," Current Research in Alzheimer's Therapy, Giacobini and Becker (eds.), pp. 295-303, 1988); methanesulfonyl. . .

DETD . . . hydrolytic enzymes for example Alkaline phosphatase, 5'-Nucleotidase, Acetylcholinesterase (AChE), Trehalase, Alkaline phosphodiesterase I, gp63 proteinase, Dipeptidase, p76 proteinase, Aminopeptidase P, **Lipoprotein** lipase; Mammalian antigens for example, Thy-1, Thy-3, RT-6, Qa, Ly-6, MEM-43, Carcinoembryonic antigen (CEA), NCA, Blast-1, MRC OX-45, CD14, Mo3,. . .

DETD . . . in or attached to viral envelopes or vesicles. Vesicles are micellular particles which are usually spherical and which are frequently **lipid**. Liposomes are vesicles formed from a bilayered membrane. Suitable vesicles include unilamellar vesicles and multilamellar **lipid** vesicles or liposomes, which may be made from a wide range of **lipid** or phospholipid compounds, such as phosphatidylcholine, phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, sphingomyelin, glycolipids, gangliosides etc. using known techniques, such as those. . .

DETD . . . of Alzheimer's Disease include substances which restore or replace cholinergic function, such as tacrine, choline, lecithin, huperzine A and B, **galanthamine**, methanesulfonyl fluoride, physostigmine and deprenyl.

DETD . . . cells was reduced drastically. This result suggests that p97 expressed on the surface of Sf9 cells is attached by a **lipid** anchor as it is in SK-MEL-28 cells.

L15 ANSWER 2 OF 6 USPATFULL

AB The present invention is concerned with the method of using a 2,3-dihydro-imidazo[2,1-b]benzothiazole derivative for the manufacture of a medicament for the therapeutic or prophylactic treatment of humans suffering from ageing of, or degenerative diseases of the nervous and vascular system which are associated with oxidative stress.

AN 1999:113771 USPATFULL

TI Use of fused benzothiazoles as neuroprotectants

IN De Brabander, Marc Joris, Zoersel, Belgium
Lesage, Anne Simone Josephine, Halle-Zoersel, Belgium
Leysen, Josepha Eduarda Maria Francisca, Oud-Turnhout, Belgium

PA Janssen Pharmaceutica, N.V., Beerse, Belgium (non-U.S. corporation)

PI US 5955485 19990921 <--
WO 9625931 19960829 <--

AI US 1997-894121 19970812 (8)
WO 1996-EP677 19960214
19970812 PCT 371 date
19970812 PCT 102(e) date

PRAI EP 1995-200446 19950223

DT Utility

FS Granted

EXNAM Primary Examiner: Ramsuer, Robert W.; Assistant Examiner: Murray, Joseph

LREP Coletti, Ellen Ciambrone

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 621

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5955485 19990921 <--
WO 9625931 19960829 <--
SUMM . . . pancreas, the parathyroid glands and the gonads. Oxidative stress in tissue cells leads to DNA damage, protein damage and to **lipid** peroxidation, the latter giving rise to changes in cell membrane integrity and function. Oxidative injury by oxygen derived free radicals. . .
SUMM . . . activity of 2,3-dihydro-imidazo[2,1-b]benzothiazole derivatives can be demonstrated in vitro by their ability to scavenge free radicals and thus prevent radical-induced **lipid** peroxidation and cytotoxicity. In cultures of neuronal cells, they can effectively substitute the known endogenous antioxidant vitamin E (.alpha.-tocopherol). The. . .
SUMM . . . Parkinson's disease, Down's syndrome, glutaric acidaemia, epilepsy, convulsive states, multi-infarct dementia, and viral-infection induced neurodegeneration, in particular neuro-AIDS encompassing dementia, **cognitive** difficulties, progressive dysarthria, ataxia, neuro- and myopathies associated with HIV infection, or any disease that involves cerebral inflammation.
SUMM . . . suffering from AIDS and in particular neuro-AIDS. Alzheimer's disease is a kind of progressive dementia which is characterized by impaired **memory**, language, visuo-spatial skills and behaviour. Neuro-AIDS is a typical condition associated with HIV infection and manifests itself as an infection. . .
SUMM . . . that substitute for the loss of neurotransmitters, such as dopaminergic loss, e.g. levodopa; but in particular the cholinergic loss, e.g. **galanthamine**, E 2020, physostygmine or tacrine; **memory**-enhancing drugs, e.g. sabeluzole; agents used in combatting AIDS such as nucleoside reverse transcriptase inhibitors,. e.g. zidovudine (AZT), didanosine (ddI), zalcitabine. . .

L15 ANSWER 3 OF 6 USPATFULL
AB A pharmaceutical composition for trans-mucosal or transdermal administration wherein a per-C.sub.2-18 acylated cyclodextrin is used as a drug reservoir or carrier. The composition can be used safely and exhibits excellent drug release behavior.
AN 1999:58919 USPATFULL
TI Acylated cyclodextrin-containing pharmaceutical composition
IN Uekama, Kaneto, Kumamoto, Japan
Hirayama, Fumitoshi, Kumamoto, Japan
Kondo, Akira, Shizuoka-ken, Japan
Ohta, Masaaki, Shizuoka-ken, Japan
Okamoto, Yasuhiro, Shizuoka-ken, Japan
Kunihiro, Haruo, Tokyo, Japan
PA Janssen Pharmaceutica, N.V., Beerse, Belgium (non-U.S. corporation)
PI US 5904929 19990518 <--
AI US 1997-886934 19970702 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Schenkman, Leonard
LREP Appollina, Mary A.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 574

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5904929 19990518 <--
SUMM On the other hand, **attention** has been drawn in recent years to the development of pharmaceuticals for the trans-mucosal or transdermal administration of drugs which. . . causing problems that long-term use is difficult. Particularly. many of absorption enhancers for drugs have generally a high solubility in **lipid**, and it is said that almost all of the above absorption enhancers interact with the adhesives in transdermal absorption compositions,. . .
DETD **lipid** regulating agents such as lovastatin, pravastatin, probucol and simvastatin;
DETD parasympathomimetics such as **galanthamine**, neostigmine, physostymine, tacrine, donepezil, ENA 713 (exelon) and xanomeline; and

L15 ANSWER 4 OF 6 USPATFULL
AB Therapeutic compositions comprising an effective amount of at least one carbonyl trapping agent alone or in combination with a therapeutically effective of a co-agent or medicament are disclosed. The compositions are used to treat a mammal suffering from a neurological disease characterized by covalent bond crosslinking between the nerve cells, other cellular structures and their intracellular and extracellular components, with disease induced carbonyl-containing aliphatic or aromatic hydrocarbons present in mammals.
AN 97:83944 USPATFULL
TI Methods of treating neurological diseases and etiologically related symptomology using carbonyl trapping agents in combination with previously known medicaments
IN Shapiro, Howard K., 214 Price Ave. F32, Narberth, PA, United States 19072
PI US 5668117 19970916 <--
AI US 1993-62201 19930629 (8)
RLI Continuation-in-part of Ser. No. US 1993-26617, filed on 23 Feb 1993, now abandoned which is a continuation of Ser. No. US 1991-660561, filed on 22 Feb 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Leary, Louise
LREP Perrella, D. J.
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3963
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5668117 19970916 <--
SUMM . . . and coworkers, 1983; Goldstein and coworkers, 1990, pg. 102; Rinne, 1991). For example, in a study on two-drug combinations of **memory** enhancing agents Flood and coworkers (1988) noted that:
SUMM The potential for clinically desirable drug interactions has been emphasized for drugs in general (1) and for **memory** enhancing drugs in particular (2,3). For example, individual cholinergic drugs which improve **memory** retention test scores (4,5,6) do so in two-drug combinations at substantially lower doses than would be predicted if the two. . .
SUMM In prior studies of the effect of two-drug combinations on **memory** processing (8,9), we determined the effect of varying the dose of two drugs while holding the ratio constant. The ratio was based on the optimal **memory** enhancing doses of each drug administered singly. These studies showed that drugs administered in certain combinations require 67 to 96%. . .

SUMM . . . ascorbic acid, alpha-tocopherol, beta-carotene (Mathews-Roth, 1987), N-acetylcysteine (Smilkstein and coworkers, 1988), penicillamine or cysteamine (Harris, 1982), as increased levels of **lipid** peroxidation are apparent in parkinsonian tissue (Ceballos and coworkers, 1990; Fahn, 1989); (f) other peripheral decarboxylase inhibitors such as benserazide. . .

SUMM . . . Ser. No. 07/660,561, filed Feb. 21, 1991, now abandoned, may serve to sequester and remove aldehyde and ketone products of **lipid** peroxidation process known to exist in parkinsonian substantia nigra tissue (Fahn, 1989; Youdim, 1990). This may at least partially address. . .

SUMM . . . areas and cerebral cortex. Moreover, amyloid formation may arise as a consequence of membrane damage . . . due to **lipid** peroxidation . . . About 6% of PHF [paired helical filaments] is composed of the amino-acid, hydroxyproline. This amino-acid is. . .

SUMM . . . and coworkers, 1988; Davies, 1991, pg. S-25), metrifonate (Becker and Giacobini, 1988), velnacrine maleate (Cooper, 1991; Cutler and coworkers, 1992), galanthamine (Nivalin) (Ferris, 1990; Sweeney and coworkers, 1990), sulfonyl fluorides such as methanesulfonyl fluoride (Moos and Hershenson, 1989) and phenylmethylsulfonyl fluoride. . .

SUMM . . . of the brain, generates H.sub.2 O.sub.2, which in turn may generate neurocytotoxic hydroxyl free radicals (HO.sup.-) and leads to subsequent **lipid** peroxidation. Hence, use of MAO-B inhibitors such as L-deprenyl may have an anti-aging clinical effect (Youdim, 1990). The use of. . .

SUMM . . . and Padilla, 1990), huperzine A (Moos and Hershenson, 1989), huperzine B (Tang and coworkers, 1989), edrophonium (Flood and coworkers, 1988), **galanthamine** (Nivalin) (Sweeney and coworkers, 1990), metrifonate (Moos and Hershenson, 1989) and velnacrine (Cutler and coworkers, 1992); (c) cholinergic muscarinic agonists. . .

SUMM . . . enzyme inhibitors such as captopril, epi-captopril and zofenopril, which also have free radical scavenging properties (Westlin and Mullane, 1988); (e) anti-**hyperlipidemia** agents such as fibric acid derivatives, including gemfibrozil (Lopid) (Garg and Grundy, 1990), bezafibrate (Olsson and Lang, 1978a; Olsson and. . .

SUMM Numerous prior art publications have disclosed that vitamin E (alpha-tocopherol) functions physiologically as a **lipid** -soluble antioxidant free radical trapping agent. Prior art publications have also described methionine as a water-soluble agent, an essential amino acid,. . . of neurodegenerative diseases by use of primary agents which are primary amine and amine-related substances to inhibit aldehyde-mediated protein and **lipid** crosslinking, said primary agents capable of being used in combination with known antioxidants and related substances as co-agents.

SUMM . . . 1980 document that vitamin C also can act physiologically as a pro-oxidant (Gutteridge and Wilkins, 1982), an agent which stimulates **lipid** peroxidation (Chojkier and coworkers, 1989, pgs. 16957 and 16961), and that it is a strong protein glycosylating agent (Ortwerth and. . .

SUMM . . . (Ylikoski and coworkers, 1980), and juvenile ceroid-lipofuscinosis (Schwendemann, 1982). Heart lipofuscin has been shown to have the following general composition: **lipids**, 20-50%; protein, 30-60%; and strongly pigmented resin-like hydrolysis-resistant material, 9-20%. Although the exact nature of the

hydrolysis-resistant chemical bonds remains. . .

SUMM The results of several published research studies suggest that dysfunctional **lipid** peroxidation may be a contributing factor in the etiology of Parkinson's disease (Fahn, 1989), multiple sclerosis (Hunter and coworkers, 1985). . .

SUMM . . . to be (1) the progressive accumulation of lipofuscin and (2) concomitant appearance of high molecular weight protein aggregates and/or polymeric **lipid**-protein complexes (Shimasaki and coworkers, 1984). Age-onset peripheral nerve damage has been recognized in both man and experimental animals. Such polyneuropathy. . .

SUMM . . . (b) cisapride (Prepulsid) (Bergmann and coworkers, 1992); (c) famotidine (Pepcid); (d) cimetidine (Tagamet); (e) ranitidine (Zantac); (f) omeprazole (Prilosec); and **galanthamine** (Sweeney and coworkers, 1990).

SUMM . . . studies showed the appearance of covalently crosslinked protein polymers during senile cataract formation (Selkoe and coworkers, 1982). Evidence of increased **lipid** peroxidation in the aged human lens has also been presented (Bhuyan and coworkers, 1986).

SUMM In addition, several published studies have presented evidence which implicates **lipid** peroxidation products in the etiology of atherosclerosis (Halliwell, 1991, pg. 583). 4-Hydroxy-2,3-transnonenal covalently binds to lysine and other peptide residues of low-density **lipoprotein** much more readily than malondialdehyde. Hence, it (as well as other aldehydes) may play a role in the etiology of. . . and coworkers, 1986; and Esterbauer and coworkers, 1987). As summarized by Steinbrecher (1987), there is reason to believe that reactive **lipid** peroxidation agents form Schiff base adducts with the lysine epsilon-amino groups of low density **lipoproteins** (LDL). Such modified LDL's are recognized by high-affinity acetyl-LDL receptors located on macrophages, which results in **lipid** accumulation. **Lipid**-laden macrophages appear to be precursors of the foam cells which populate early atherosclerotic lesions (Steinbrecher, 1987).

Use of the invention. . . provide additional clinical benefit for patients suffering from these chronic, age-related diseases. Previously recognized drugs for treatment of atherosclerosis include **hypolipidemic** agents such as fenofibrate (Elsom and coworkers, 1976; Wulfert and coworkers, 1976), bezafibrate (Olsson and Lang, 1978a;

Olsson and Lang,. . .

SUMM . . . that 5-hydroxymethyl-2-furfural and 2,5-furandialdehyde can originate as by-products of either of two general areas of metabolism, that of sugars and **lipids**. The thought that secondary products of **lipid** peroxidation might include metabolites such as 5-hydroxymethyl-furanaldehyde and 2,5-furandialdehyde has attracted little, if any, **attention** within the biomedical research community prior to submission of U.S. patent application Ser. No. 07/660,561, filed Feb. 21, 1991, now. . .

SUMM . . . clinical value in the treatment of disease symptomology for disorders featuring well defined neurofilament associated pathology, lipofuscin accumulation and/or aberrant **lipid** peroxidation, including: diabetic polyneuropathy and related metabolic symptomology; Alzheimer's presenile/senile dementia; Down's syndrome; Parkinson's disease; amyotrophic lateral sclerosis; age-related atrophy. . .

SUMM It is a further object of this invention to draw **attention** to and originally recognize that the appearance of one or more chromosome 17 HMSN-specific cultured fibroblast proteins may be used. . .

SUMM Use of absorbable amine and amine-related primary agents, non-absorbable

amine and amine-related co-agents, co-agents which inhibit **lipid** peroxidation, human growth hormone co-agent, vitamin co-agents which may be inadvertently depleted, co-agent metabolites such as glycine which may be. . .

SUMM . . . normal intracellular structures is a fundamental aspect of the neurological diseases addressed herein. Such covalent bond crosslinking of protein and **lipid** subcellular elements appears to underlie the formation of at least four common neuropathological structures: (1) polymerized aggregates of structural protein filaments (e.g., excess neurofilament accumulation), (2) heterogeneous protein aggregates (e.g., neurofibrillary tangles), (3) amorphous protein and **lipid** aggregates (e.g., senile plaques), and (4) lipofuscin granules, which are amorphous aggregates rich in **lipid** chemical complexes. Spurious, excess protein chemical crosslinking is also apparent in the extracellular compartment in some of these diseases, for. . .

SUMM Moving to the chemical level, considerable biomedical literature indicates that certain sites on normal proteins and **lipids** are specific targets for spurious chemical crosslinking, most notably the epsilon-amino groups of lysine residues in proteins and the amine groups of phosphatidylethanolamine molecules in cell **lipid** membrane bilayers. These primary amine groups are especially prone to attack by small molecular weight carbonyl-containing hydrocarbons. Such carbonyl-containing molecules. . . from peroxidation of fatty acids or as by-products of sugar metabolism. A monocarbonyl specie can bind to a protein or amino-**lipid**, alter its three dimensional structure and possibly affect its chemical activity. A dicarbonyl hydrocarbon can react with two amine groups,. . .

SUMM Kikugawa and Beppu (1987) noted that **lipid** radicals, hydroperoxides and their secondary products react with neighboring protein molecules, damaging protein structure and function. Such damage includes formation of fluorescent chromophores, **lipid**-protein adducts, and protein-protein crosslinks. Using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, these investigators demonstrated that malonaldehyde (also known as malondialdehyde), a. . .

SUMM The generation of water soluble, carbonyl-containing products of **lipid** peroxidation can be readily demonstrated under simple in vitro conditions. Schauenstein (1967) incubated suspended polyunsaturated fatty acid esters with water. . . water soluble products not characterized in Schauenstein's investigation. Other investigators have also documented the generation of numerous carbonyl-containing products of **lipid** peroxidation, however the exact identities of many of these agents remains undefined (Esterbauer and coworkers, 1982).

SUMM The conceptual similarities between **lipid** peroxidation-induced protein crosslinking and protein crosslinking associated with non-enzymatic glycosylation has been noted in the research literature (Kikugawa and Beppu, 1987). Some evidence has been presented which suggests that a slow, age-dependent deterioration of biological systems which counteract **lipid** peroxidation may be a fundamental part of the aging process (Harman, 1971). This concept is sometimes referred to as the. . .

SUMM . . . furan, other alkyl furans, and a variety of five- to eight-carbon alkyl aldehydes and ketones. Yancey and coworkers (1986) induced **lipid** peroxidation in rats by use of a defined diet deficient in both vitamin E and selenium, and then studied volatile. .

SUMM . . . and LC results appear to implicate aldehydes (both normal and unsaturated) and related compounds, furan derivatives, as characteristic products of **lipid** peroxidation. Elevated aldehyde levels were also noticed in our earlier investigations of urinary metabolites of both long-term diabetic rats and genetically diabetic mice. Since an increased **lipid** peroxidation process has been associated with the diabetic condition, it is not surprising that known peroxidation metabolites should be more abundant in diabetic than normal urine samples . . . Increased **lipid** peroxidation clearly results in a greater production of metabolites that are either proven or suspected neurotoxins.

SUMM . . . U.S. patent application Ser. No. 08/026,617, filed Feb. 23, 1993, now abandoned, 2,5-dimethyl furan is a recognized secondary product of **lipid** peroxidation and there is reason to believe that it may be oxidized in vivo to products such as 5-hydroxymethyl-2-furancarboxylic acid. . .

SUMM . . . the unique belief and understanding of this inventor that the long term generation of furan aldehyde agents as by-products of **lipid** peroxidation can serve as a metabolic basis or underlying contributing factor in the etiology of diabetic symptomology, the etiology of. . . long term consequences of furanaldehyde exposure as a consequence of defective ability to oxidize furanaldehydes which are normal products of **lipid** metabolism. Failure to dispose of these reactive metabolites efficiently may predispose the patients to pathological events initiated by spurious protein. . .

SUMM . . . molecular weight primary amine agents and chemical derivatives thereof. Such pharmacological agents, administered orally, can compete with cellular protein and **lipid** amine groups for reaction with disease-induced carbonyl-containing hydrocarbons. Such derivatized pharmacological agents can then be excreted by the kidneys. This. . .

DETD **galanthamine**, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily; and

DETD (d) anti-**hyperlipidemia** agents such as

DETD **galanthamine**, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily; and

DETD (g) **galanthamine**, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily.

DETD (b) fibric acid derivative anti-**hyperlipidemia** agents such as

DETD Anand, R. and Wesnes, K. A. "**Cognition**-enhancing effects of moclobemide, a reversible MAO inhibitor, in humans" Adv. Neurol. 51:261-268 (1990)

DETD Ananth, J. et al. "Cyclandelate therapy for **memory** disorders" Curr. Ther. Res. 38:627-631 (1985)

DETD Baratti, C. M. et al. "Possible interaction between central cholinergic muscarinic and opioid peptidergic systems during **memory** consolidation in mice" Behav. Neural Biol. 40:155-169 (1984)

DETD Bartus, R. T. and Dean, R. L. "Tetrahydroaminoacridine, 3,4-diaminopyridine and physostigmine: direct comparison of effects on **memory** in aged primates" Neurobiol. Aging 9:351-356 (1988)

DETD Bhuyan, K. C. et al. "**Lipid** peroxidation in cataract of the human" Life Sci. 38:1463-1471 (1986)

DETD Clincke, G. H. et al. "The effect of R 58 735 (Sabeluzole) on **memory** functions in healthy elderly volunteers" Psychopharmacology 94:52-57 (1988)

DETD Crook, T. H. "Assessment of drug efficacy in age-associated **memory** impairment" Adv. Neurol. 51:211-216 (1990)

DETD Crook, T. H. and Larrabee, G. J. "Diagnosis, assessment and treatment of

age-associated **memory** impairment" J. Neurol. Transm. 33[Suppl]:1-6 (1991)
DETD Cumin, R. et al. "Effects of the novel compound aniracetam (Ro 13-5057) upon impaired learning and **memory** in rodents" Psychopharmacology 78:104-111 (1982)
DETD Davis, K. L. et al. "Physostigmine: improvement of long-term **memory** processes in normal humans" Science 201:272-274 (1978)
DETD Durrington, P. N. "Specific **lipid** lowering therapy in the management of diabetes" Postgrad. Med. J. 67:947-952 (1991)
DETD Esterbauer, H. et al. "Separation and characterization of the aldehydic products of **lipid** peroxidation stimulated by ADP-Fe2.sup.+ in rat liver microsomes" Biochem. J. 208:129-140 (1982)
DETD Esterbauer, H. et al. "Autoxidation of human low density **lipoprotein**: Loss of polyunsaturated fatty acids and vitamin E and generation of aldehydes" J. **Lipid** Res. 28:495-509 (1987)
DETD Flood, J. F. et al. "Two-drug combinations of **memory** enhancers: effect of dose ratio upon potency and therapeutic window, in mice" Life Sci. 42:2145-2154 (1988)
DETD Garg, A. and Grundy, S. M. "Management of **dyslipidemia** in NIDDM" Diabetes Care 13:153-169 (1990)
DETD Groo, D. et al. "Effects of vinpocetine in scopolamine-induced learning and **memory** impairments" Drug Dev. Res. 11:29-36 (1987)
DETD Hindmarch, I. and Subhan, Z. "A preliminary investigation of `Albert 285` (HWA 285) on psychomotor performance, mood, and **memory**" Drug Dev. Res. 5:379-386 (1985)
DETD Hjelle, J. J. and Petersen, D. R. "Hepatic aldehyde dehydrogenases and **lipid** peroxidation" Pharmacol. Biochem. Behav. 18:155-160 (1983)
DETD Hock, F. J. and McGaugh, J. L. "Enhancing effects of Hoe 175 on **memory** in mice" Psychopharmacology 86:114-117 (1985)
DETD Hock, F. J. et al. "Learning and **memory** processes of an ACTH.sub.4-9 analog (ebiratide; Hoe 427) in mice and rats" Peptides 9:575-581 (1988)
DETD Hunter, M. I. et al. "**Lipid** peroxidation products and antioxidant proteins in plasma and cerebrospinal fluid from multiple sclerosis patients" Neurochem. Res. 10:1645-1652 (1985)
DETD Hunter, M. I. and Mohamed, J. B. "Plasma antioxidants and **lipid** peroxidation products in Duchenne muscular dystrophy" Clin. Chim. Acta 155:123-132 (1986)
DETD Jensen, R. A. et al. "**Memory**, opiate receptors, and aging" Peptides 1[Suppl. 1]:197-201 (1980)
DETD Jensen, L. H. et al. "Bidirectional effects of beta-carbolines and benzodiazepines on **cognitive** processes" Brain Res. Bull. 19:359-364 (1987)
DETD Jurgens, G. et al. "Modification of human low-density **lipoprotein** by the **lipid** peroxidation product 4-hydroxynonenal" Biochim. Biophys. Acta 875:103-114 (1986)
DETD Kikugawa, K. and Beppu, M. "Involvement of **lipid** oxidation products in the formation of fluorescent and cross-linked proteins" Chem. Phys. **Lipids** 44:277-296 (1987)
DETD . . . B. C. et al. "Placebo-controlled trial of the effects of guar gum and metformin on fasting blood glucose and serum **lipids** in obese, type 2 diabetic patients" Diabetic Med. 7:242-245 (1990)
DETD Lovisolo, P. P. et al. "Pharmacological profile of a new antilipolytic agent: 5-methylpyrazine-2-carboxylic acid 4-oxide (acipimox). II-Antilipolytic and blood **lipid** lowering activity" Pharmacol. Res. Commun. 13:163-174 (1981)
DETD Micheau, J. et al. "Chronic administration of sulbutiamine improves long
term **memory** formation in mice: possible cholinergic mediation" Pharmacol. Biochem. Behav. 23:195-198 (1985)

DETD Moos, W. H. et al. "**Cognition** activators" Med. Res. Rev. 8:353-391 (1988)

DETD Moos, W. H. and Hershenson, F. M. "Potential therapeutic strategies for senile **cognitive** disorders" Drug New Perspective 2:397-409 (1989)

DETD Olsson, A. G. and Lang, P. D. "Dose-response study of bezafibrate on serum **lipoprotein** concentrations in hyperlipoproteinaemia" Atherosclerosis 31:421-428 (1978a)

DETD Olsson, A. G. and Lang, P. D. "One-year study of the effect of bezafibrate on serum **lipoprotein** concentrations in hyperlipoproteinaemia" Atherosclerosis 31:429-433 (1978b)

DETD Schauenstein, E. "Autoxidation of polyunsaturated esters in water: Chemical structure and biological activity of the products" J. **Lipid** Res. 8:417-428 (1967)

DETD Shimasaki, H. et al. "Formation of age pigment-like fluorescent substances during peroxidation of **lipids** in model membranes" Biochim. Biophys. Acta 792:123-129 (1984)

DETD Shimizu, M. "Current clinical trials of **cognitive** enhancers in Japan" Alzheimer's Dis. Assoc. Disord. 5[Suppl. 1]:S13-S24 (1991)

DETD Spignoli, G. et al. "Effect of pyroglutamic acid stereoisomers on ECS and scopolamine-induced **memory** disruption and brain acetylcholine levels in the rat" Pharmacol. Res. Commun. 19:901-912 (1987)

DETD Steinbrecher, U. P. "Oxidation of human low density **lipoprotein** results in derivatization of lysine residues of apolipoprotein B by **lipid** peroxide decomposition products" J. Biol. Chem. 262:3603-3608 (1987).

DETD Stern, M. P. and Haffner, S. M. "**Dyslipidemia** in type II diabetes--implications for therapeutic intervention" Diabetes Care 14: 1144-1159 (1991)

DETD Sweeney, J. E. et al. "Effects of different doses of **galanthamine**, a long-acting acetylcholinesterase inhibitor, on **memory** in mice" Psychopharmacology 102:191-200 (1990)

DETD Thal, L. J. and Altman Fuld, P. "**Memory** enhancement with oral physostigmine in Alzheimer's disease" N. Engl. J. Med. 308:720 (1983)

DETD Thal, L. J. et al. "Chronic oral physostigmine without lecithin improves **memory** in Alzheimer's disease" J. Am. Geriatr. Soc. 37:42-48 (1989)

DETD Tsuchida, M. et al. "Lipofuscin and lipofuscin-like substances" Chem. Phys. **Lipids** 44:297-325 (1987)

DETD . . . 178 in man. A preliminary note on a multicenter investigation bearing on 393 subjects with pure or mixed forms of **hyperlipidemia**" Arzneim.-Forsch./Drug Res. 26:906-909 (1976)

DETD Yancey, M. et al. "Quantitative alterations in the metabolism of carbonyl compounds due to diet-induced **lipid** peroxidation in rats" J. Chromatogr. 382:47-56 (1986)

CLM What is claimed is:

. . . one of the following medicaments: (a) insulin derivatives and compositions; (b) sulfanilamide derivative hypoglycemic agents; (c) angiotensin-converting enzyme inhibitors; (d) anti-**hyperlipidemia** co-agents; (e) antioxidants; (f) immunosuppressive drugs; (g) co-agents which decrease blood platelet aggregation; (h) co-agents which decrease blood viscosity; (i). . .

. . . least one of the following medications: (a) metoclopramide; (b) cisapride; (c) famotidine; (d) cimetidine; (e) ranitidine; (f) omeprazole; and (g) **galanthamine**, wherein the composition is adapted to administer both the carbonyl trapping primary amine and the medicament via the same route.

. . .

. . . the following medicaments: (a) an angiotensin-converting enzyme inhibitor free radical scavenging co-agent possessing sulfhydryl groups;
(b) a fibric acid derivative anti-**hyperlipidemia** co-agent; (c) metformin; (d) nicotinic acid; (e) a natural hydroscopic non-digestable edible plant carbohydrate polymer; (f) 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors; (g). . .

IT 50-18-0, Cyclophosphamide 54-96-6, 3,4-Diaminopyridine 56-40-6, Glycine, biological studies 57-47-6, Physostigmine 58-56-0, Pyridoxine hydrochloride 58-85-5, Biotin 59-02-9 59-30-3, Folic acid, biological studies 59-43-8, Thiamine, biological studies 59-51-8, D,L-Methionine 59-67-6, Nicotinic acid, biological studies 59-92-7, Levodopa, biological studies 68-19-9, Vitamin B12 68-41-7, D-Cycloserine 72-19-5, L-Threonine, biological studies 79-83-4, Pantothenic acid 83-88-5, Vitamin B2, biological studies 98-92-0, Nicotinamide 137-08-6 137-58-6, Lidocaine 150-13-0, p-Aminobenzoic acid 302-79-4D, Retinoic acid, derivs. 302-84-1, Serine 321-64-2, Tacrine **357-70-0**, Galanthamine 364-62-5, Metoclopramide 446-86-6, Azathioprine 456-59-7, Cyclandelate 504-24-5, 4-Aminopyridine 645-88-5, Aminooxyacetic acid 657-24-9, Metformin 768-94-5, Amantadine 1134-47-0, Baclofen 1195-16-0 1406-18-4, Vitamin E 3200-06-4, Praxilene 3286-46-2, Sulbutiamine 4759-48-2, 13-cis-Retinoic acid 7235-40-7, .beta.-Carotene 7491-74-9, Piracetam 7782-49-2, Selenium, biological studies 8059-24-3, Vitamin B6 9004-10-8D, Insulin, derivs., biological studies 11000-17-2D, Vasopressin, analogs 13345-51-2D, Prostaglandin B1, oligomers 14611-51-9, Selegiline 15301-69-6, Flavoxate 18601-90-6, Thiamine mononitrate 23210-56-2, Ifenprodil 24305-27-9, Thyrotropin releasing factor 28704-27-0 28860-95-9, Carbidopa 37758-47-7, Ganglioside GM1
41708-72-9, Tocainide 51012-32-9, Tiapride 51037-30-0, Acipimox 51481-61-9, Cimetidine 54143-55-4, Flecainide 59865-13-3, Cyclosporine 66357-35-5, Ranitidine 72432-10-1, Aniracetam 73590-58-6, Omeprazole 76824-35-6, Famotidine 81098-60-4, Cisapride 103878-84-8, Lazabemide 105431-72-9, Linopirdine 196966-12-8, Anfacine
(carbonyl trapping agent combination with other drug for treatment of neurol. diseases and etiol. related symptomol.)

L15 ANSWER 5 OF 6 USPATFULL

AB Mania is treated by administering, to a patient in need thereof, **galanthamine** or a salt or derivative thereof or a functional equivalent of **galanthamine**, the functional equivalent being an acetylcholinesterase inhibitor which is active substantially selectively at nicotinic receptor sites.

AN 94:68763 USPATFULL

TI Method of treating mania in humans

IN Snorrason, Ernir, Stigahlid 80, IS-105 Reykjavik, Iceland

PI US 5336675 19940809 <--

AI US 1992-842322 19920228 (7)

PRAI IS 1991-3706 19910514
IS 1991-3706 19910731
DK 1992-183 19920213

DT Utility

FS Granted

EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner: Jordan, Kimberly R.

LREP Foley & Lardner

CLMN Number of Claims: 18

ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 917
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5336675 19940809 <--
AB Mania is treated by administering, to a patient in need thereof, **galanthamine** or a salt or derivative thereof or a functional equivalent of **galanthamine**, the functional equivalent being an acetylcholinesterase inhibitor which is active substantially selectively at nicotinic receptor sites.
SUMM According to the present invention, it has been found that mania in humans can be effectively treated by administration of **galanthamine**, and that **galanthamine** seems to not only mask the symptoms, but to provide real improvement and disappearance of symptoms faster than the usual. . .
SUMM **Galanthamine** is a well-known acetylcholinesterase inhibitor which is active substantially selectively at nicotinic receptor sites and has substantially no effect on. . .
SUMM **Galanthamine** and acid addition salts thereof have, for many years, been known to have anticholinesterase properties.
SUMM **Galanthamine**, a tertiary alkaloid, has been isolated form the bulbs of the Caucasian snowdrops Galantanus woronowi (Proskurnina, N. F. and Yakoleva,. . .
SUMM **Galanthamine** has been used extensively as a curare reversal agent in anaesthetic practice in Eastern bloc countries (cf. review by Paskow,. . . .
SUMM Pharmacokinetic studies have recently been made by Thomsen, T. and H. Kewitz. (Selective Inhibition of Human Acetylcholinesterase by **Galanthamine** in vitro and in vivo. Life Sciences, Vol 46, pp. 1553-1558 (1990), and, by the same authors, **Galanthamine** Hydrobromide in a Long-Term Treatment of Alzheimer's Disease. Dementia 1990, 1:46-51).
SUMM . . . in accordance with the above-mentioned 1973 findings by Janowski et al., the only prior art reference reporting treatment, in that **galanthamine** is an acetylcholinesterase inhibitor, such as is physostigmine, and thus counteracts cholinergic deficiency. On the other hand, physostigmine, used by Janowsky, has a profile of properties which is basically different from the profile of **galanthamine**. Thus, physostigmine, contrary to **galanthamine**, has a considerable effect at muscarinic receptor sites, and has a very fast onset of activity and a very short. . .
SUMM It is believed that the excellent and suprising effect against mania possessed by **galanthamine** is due to its specific profile of properties, the most important of the known ones of which can be summarized. . .
SUMM **Galanthamine** must be considered as being a very desirable drug for the treatment according to the invention: The elimination half life of **galanthamine** hydrobromide is over four hours; it shows a practically complete renal elimination; its two metabolites, epigalanthamine and galanthaminone are both probably inactive. A complete elimination of metabolites and **galanthamine** takes place in 72 hours. **Galanthamine** has been used in Eastern Block countries since around 1958 as an anticurare agent in anesthesiology, and a considerably number of patients have been treated with **galanthamine** without any reported case of liver toxicity or serious side effects. **Galanthamine** hydrobromide, being a

tertiary amine and **lipid** soluble, is absorbed rapidly from the gut and transverses the blood brain barrier easily. The common side effects, other than. . .

SUMM . . . new hypomanic/manic phase or the duration thereof. This means that it is of great importance to have a drug, like **galanthamine**, which has an onset of action of as little as a few minutes.

SUMM . . . for the treatment of mania in humans, comprising administering, to a human patient in need thereof, an effective amount of **galanthamine**.

SUMM The **galanthamine** can suitably be administered orally in the form of an acid addition salt, e.g. the hydrobromide, but other administration forms. . .

SUMM . . . meaning of this term, e.g. such as lithium is administered for prophylacting mania, would normally not come into consideration because **galanthamine** and functional equivalents have a fast onset of action.

SUMM Because **galanthamine** has substantially no effect on the activity at muscarinic receptor sites, as apparent from its high selectivity for acetylcholinesterase as. . . on the heart which are associated with cholinesterase inhibitors which have a low selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. **Galanthamine** has a selectivity for acetylcholinesterase opposed the effect on butyrylcholinesterase of 60 to 1.

SUMM The amount of **galanthamine** is preferably adjusted individually based upon observation of the effect of initially very low dosages. There is as considerable difference with respect to how sensitive individuals are to acetylcholinesterase inhibitors. Thus, the amount of **galanthamine** is suitably adjusted by means of a regimen starting at low dosages, e.g. 1 mg, preferably at 5 mg, per. . . per day dosed over 3 or 4 times. The increase of the dosages is suitably discontinued when the dosage of **galanthamine**

SUMM The effect of the **galanthamine** against the patient's mania is suitably measured by scoring the symptoms of the patients in accordance with the guidelines in. . .

SUMM . . . the patients according to Bech's mania Scale. When the patients have reached a score below 6, they are kept on **galanthamine** medication for about another two months to be sure that the patient is properly treated.

SUMM As far as is known, **galanthamine** is the only acetylcholinesterase inhibitor with the above-defined profile of properties which has been tested against mania in humans. While **galanthamine** has, indeed, given remarkable results, such as appears from the clinical data given in the examples, it is justified to presume that other acetylcholinesterase inhibitors which are functional equivalents to **galanthamine** with respect to its combination of high selectivity with respect to nicotinic receptor sites and capability of passing the blood. . . show a useful combination of effect against mania and acceptability in the clinic, although it cannot be ruled out that **galanthamine**, **galanthamine** salts and **galanthamine** derivatives, due to the special conformation of the gelanthamine ring system, have specific properties which are decisive for the remarkable. . .

SUMM In accordance with the above, compounds which are functional equivalents

of **galanthamine** are defined herein as compounds which

SUMM . . . humans. Both of these tests give further indication of whether the candidate drug has a spectrum of properties equivalent to **galanthamine** with respect to what must be presumed to be essential properties. Peripheral side effects will be assessable when the effect. . . and especially the well-defined in vitro character of

the initial screening, the test series for identifying useful functional

equivalents of **galanthamine** is a reasonable an not burdensome routine which is within the realm of the person skilled in the art.

SUMM Functional equivalents and derivatives of **galanthamine** which are useful in the method of the invention will be employed in the same manner as stated herein for **galanthamine**. Whenever quantities of such a functional equivalent or derivative are referred to herein, the quantities are given as the equipotent quantity of **galanthamine** hydrobromide with respect to inhibition of acetylcholinesterase, that is, as the quantity of **galanthamine** hydrobromide which result in the same inhibition of acetylcholine esterase in the above-mentioned in vitro test according to Thomsen et. . .

SUMM . . . in vivo tests as described by Thomsen and Kewitz in the above mentioned paper Selective Inhibition of Human Acetylcholinesterase by **Galanthamine** in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and T. Thomsen, H. Kewitz and O. Pleul,. . . selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrycholinesterase. For **galanthamine**, these authors found a 50-fold to 60-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase.

SUMM . . . . as an additional characterization, optionally be expressed with

reference to the in vivo determinations performed by Thomsen and Kewitz on **galanthamine** and described in the above-mentioned paper Selective Inhibition of Human Acetylcholinesterase by **Galanthamine** in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990). With reference to this determination, a preferred acetylcholinesterase. . . . in inhibition of at least 50% of the acetylcholinesterase activity in erythrocytes from the adult within about 2-5 minutes. For **galanthamine**, Thomsen and Kewitz found 65% inhibition of acetylcholinesterase in the erythrocytes within 2 minutes after administration of 10 mg of **galanthamine** i.v. in a healthy volunteer, whereas no inhibition of butyrycholinesterase in plasma was seen. Compounds which are contemplated to be valuable functional equivalents of **galanthamine** and useful in the treatment according to the invention are the **galanthamine** derivatives having the formula I (formula I also represent **galanthamine** itself) ##STR1## wherein R.sup.1 and R.sup.2 which may be the same or different each represents a hydrogen atom or an. . .

SUMM Other compounds which are contemplated to be valuable functional equivalents useful in the method of the invention are **galanthamine** derivatives of the general formula II ##STR2## wherein the broken line represents an optionally present double bond in one or. . . .

SUMM **Galanthamine**, **galanthamine** derivatives and **galanthamine** functional equivalents, when suited therefor, may be administered orally at a dosage of e.g. 5-150 mg per day, such as. . .

. often be started with a low dosage and then increased until the suitable dosage has been established. The dosage of **galanthamine** functional equivalents is expressed as the equipotent amount of **galanthamine** hydrobromide, the reference basis being the capability of inhibiting acetylcholinesterase in the Thomsen et al. in vitro test mentioned above.

SUMM For the oral administration, **galanthamine** or a **galanthamine** salt or derivative or a functional equivalent may be formulated, for example, as an aqueous suspension or a solution in. . . are typically of a concentration of 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 10-40 mg/ml, typically 20-30 mg/ml of **galanthamine**. Divided doses in the range 0.1-3 mg/kg body weight per day may prove useful. Typically, one might administer a dosage. . .

SUMM **Galanthamine** and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable. . . employed at a concentration of 0.1-30 mg/ml, more commonly 1-30 mg/ml, for example, 5-30 mg/ml, such as 10-30 mg/ml of **galanthamine**. As mentioned above, typical dosage rates when administering **galanthamine** by injection are the range 0.01-20 mg per day depending upon the patient. For example, divided doses in the range. . .

SUMM **Galanthamine** and its pharmaceutically acceptable acid addition salts, and its derivatives and functional equivalents, when suited therefor, may be administered by. . .

SUMM The parenteral dosage rate of **galanthamine** can also be expressed by reference to the body weight of the patient; in this case, a normal dosage rate. . .

SUMM . . . techniques may be employed. If desired, a pharmaceutically acceptable carrier such as starch or lactose may be used in preparing **galanthamine** or **galanthamine** equivalent tablets. Capsules may be prepared using soft gelatine as the encapsulating agent.

If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of **galanthamine** or functional equivalents thereof which release the contents over a period of several hours thereby maintaining a constant level of **galanthamine** or its functional equivalent in the patient's blood.

SUMM Other interesting administration forms of **galanthamine** and functional equivalents are suppositories, a slow-release plaster, and other depot compositions.

SUMM Although **galanthamine** must be considered as having a high degree of safety, there have been certain side effects in a few of. . .

DETD Formulation of tablets containing **galanthamine**

DETD

Composition of 1 tablet containing 1 mg **galanthamine**

Galanthamine hydrobromide	0.001 g
Calcium phosphate	0.032 g
Lactose	0.005 g
Wheat Starch	0.0056 g
Microcrystalline Cellulose	0.015 g
Talc	0.0007 g
Magnesium Stearate	0.0007 g

DETD

Composition of 1 tablet containing 5 mg **galanthamine**

Galanthamine hydrobromide	0.005 g
Calcium phosphate	0.024 g
Lactose	0.004 g
Wheat Starch	0.004 g
Microcrystalline Cellulose	0.04 g
Talc	0.002 g
Magnesium Stearate	0.001 g

DETD

Composition of 1 tablet containing 10 mg **galanthamine**

Galanthamine hydrobromide	0.010 g
Lactose	0.040 g
Wheat Starch	0.0234 g
Microcrystalline Cellulose	0.0374 g
Talc	0.0036 g
Magnesium Stearate	0.0012 g
Gelatin	0.0044 g

DETD Clinical trials of the effect of **galanthamine** on manic patients

DETD Nivalin tablets containing 5 mg **galanthamine**, obtained from Waldheim Ltd., Vienna, Austria, were used in this example.

DETD . . . before the treatment to exclude patients with mania-like symptoms caused by a disease of organic origin from the treatment with **galanthamine** and were also performed during the treatment in order to document any alterations of the parameters during the treatment with. . .

DETD . . . augmented depression disappeared later although he continued on the Nivalin treatment. And he felt that the Nivalin treatment improved his **memory** which he had felt were failing him.

DETD . . . five cases are all chronically ill patients with advanced affective disorder. The cases show the value of the treatment of **galanthamine** in manic patients.

DETD Tablet containing 10 mg **galanthamine**

DETD From the results in the depressed person it is seen that the potentials change after treatment with **galanthamine**, such as explained above. This means that **galanthamine** must be able to cross the blood-brain barrier, since it is possible to inhibit in synapsis in the brain stem,. . .

DETD . . . shows the auditory evoked response of a depressed patient (a manio depressed patient in the depressed state) without treatment with **galanthamine**.

DETD . . . evoked response of a depressed patient (the same as in FIG. 1A) 2 hours after treatment with 10 mg of **galanthamine**.

DETD FIG. 2A shows the auditory evoked response of a healthy person without treatment with **galanthamine**.

DETD . . . evoked response of a healthy person (the same as in FIG. 2A) 2 hours after treatment with 10 mg of **galanthamine**.

CLM What is claimed is:

8. A method according to claim 1, in which the cholinesterase inhibitor is **galanthamine**, a **galanthamine** salt, or a **galanthamine** derivative.

9. The method of claim 1, wherein the cholinesterase inhibitor is **galanthamine** or a salt thereof.

. . . which the acetylcholinesterase inhibitor is administered at a dosage of 0.1-150 mg per day, calculated as the equipotent quantity of **galanthamine** hydrobromide.

. . . which the acetylcholinesterase inhibitor is administered at a dosage of 5-60 mg per day, calculated as the equipotent quantity of **galanthamine** hydrobromide.

. . . which the cholinesterase inhibitor is administered at a dosage of 10-40 mg per day, calculated as the equipotent quantity of **galanthamine** hydrobromide.

14. A method according to claim 9, wherein the salt is **galanthamine** hydrobromide.

15. A method according to claim 9, in which the **galanthamine** is administered at a dosage of 0.1-150 mg per day.

16. A method according to claim 15, in which the **galanthamine** is administered at a dosage of 5-60 mg per day.

17. A method according to claim 16, in which the **galanthamine** is administered at a dosage of 10-40 mg per day.

18. A method according to claim 9, in which the amount of the **galanthamine** is established by increasing the dosage from 1 mg daily until the dosage positions the patient in a condition of. . .

IT 52-68-6 57-47-6 321-64-2 321-64-2D, analogs **357-70-0**, Galanthamine 1668-85-5 16088-19-0 41303-74-6 51581-32-9 86697-68-9, Fasciculin 101246-68-8 102518-79-6
(benzodiazepines hypnotic and sedative activity inhibition by, in humans)

L15 ANSWER 6 OF 6 USPATFULL

AB The use of a pharmaceutically acceptable cholinesterase inhibitor or a prodrug therefor for the treatment of fatigue syndromes, including chronic fatigue syndrome, post-infectious fatigue syndromes, fatigue syndromes associated with human immunodeficiency virus (HIV) infection or with preeclampsia. The acetyl cholinesterase is preferably one that acts substantially selectively at nicotinic receptor sites, and which has selectivity for acetyl cholinesterase as opposed to butyryl cholinesterase. Compounds of the invention include **galanthamine** and **galanthamine** derivatives.

AN 94:42345 USPATFULL

TI Treatment of fatigue syndrome

IN Snorrason, Ernir, Stigahlid 80, 105 Reykjavik, Iceland

PI US 5312817 19940517 <--

AI US 1992-883038 19920514 (7)

PRAI IS 1991-370691 19910514
DK 1992-181 19920213

DT Utility

FS Granted

EXNAM Primary Examiner: Waddell, Frederick E.; Assistant Examiner: Criares, T.

J.
LREP Foley & Lardner
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1257
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5312817 19940517 <--
AB . . . nicotinic receptor sites, and which has selectivity for acetyl cholinesterase as opposed to butyryl cholinesterase. Compounds of the invention include **galanthamine** and **galanthamine** derivatives.
SUMM . . . as fatigue associated with pre-eclampsia. Preferably, the cholinesterase inhibitors are selected from a group of nicotinic acetylcholinesterase inhibitors such as **galanthamine** -hydrobromide, which are able to cross the blood brain barrier in humans.
SUMM . . . salt of inositephosphoric acid, 10 to 12% by weight of lyophilized hydrolysate of Royal Jelly, and 1 to 3% of **galanthamine**. The present invention does not encompass such tonic. EP 098 975 does not describe any phenomenon which corresponds to fatigue. . .
SUMM It has now been found that on administration of **galanthamine**, a cholinesterase inhibitor, the fatigue disappears, the time for disappearance of the fatigue generally being proportionate to the time the. . .
SUMM . . . preferably one which crosses the blood-brain barrier and furthermore is selective with respect to cholinergic nicotinic receptor sites, such as **galanthamine** hydrobromide.
SUMM Pharmaceutically acceptable cholinesterase inhibitors are, e.g., **galanthamine** and **galanthamine** derivatives, norgalanthamine and norgalanthamine derivatives, epigalanthamine and **galanthamine**, physostigmine, tacrine and tacrine analogues, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, and huperzine or a prodrug therefor. Some of the cholinesterase. . . capability of the compound to pass the blood-brain barrier. The presently preferred cholinesterase inhibitor used according to the invention is **galanthamine**. **Galanthamine** is known as an acetylcholinesterase acting substantially only at nicotinic receptor sites, that is, having a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. A more detailed discussion of **galanthamine** and **galanthamine** derivatives is given below:
SUMM **Galanthamine** is a well-known acetylcholinesterase inhibitor which is active substantially selectively at nicotinic receptor sites and has substantially no effect on. . .
SUMM **Galanthamine** and acid addition salts thereof have, for many years, been known to have anticholinesterase properties.
SUMM Galanthamine, a tertiary alkaloid, has been isolated form the bulbs of the Caucasian snowdrops Galanthanus woronowi (Proskurnina, N. F. and Yakoleva, . . .
SUMM **Galanthamine** has been used extensively as a curare reversal agent in anaesthetic practice in Eastern bloc countries (cf. review by Paskow, . . .
SUMM Pharmacokinetic studies have recently been made by Thomsen, T. and H. Kewitz. (Selective Inhibition of Human Acetylcholinesterase by **Galanthamine** in vitro and in vivo. Life Sciences, Vol 46, pp. 1553-1558 (1990), and, by the same authors, **Galanthamine**

Hydrobromide in a Long-Term Treatment of Alzheimer's Disease. Dementia 1990, 1:46-51). .

SUMM It is believed that the excellent and surprising affect possessed by **galanthamine** is due to its specific profile of properties, the most important of the known ones of which can be summarized. . .

SUMM **Galanthamine** must be considered as being a very desirable drug for the treatment according to the invention: The elimination half life of **galanthamine** hydrobromide is over four hours; it shows a practically complete renal elimination. A complete elimination of metabolites and **galanthamine** takes place in 72 hours. **Galanthamine** has been used in Eastern Block countries since around 1958 as an anticurare agent in anesthesiology, and a considerably number of patients have been treated with **galanthamine** without any reported case of liver toxicity or serious side effects. **Galanthamine** hydrobromide, being a tertiary amine and **lipid** soluble, is absorbed rapidly from the gut and transverses the blood brain barrier easily. The common side effects, other than. . .

SUMM The **galanthamine** can suitably be administered orally in the form of an acid addition salt, e.g. the hydrobromide, but other administration forms. . .

SUMM Because **galanthamine** has substantially no effect on the activity at muscarinic receptor sites, as apparent from its high selectivity for acetylcholinesterase as. . . on the heart which are associated with cholinesterase inhibitors which have a low selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. **Galanthamine** has an in vitro selectivity for acetylcholinesterase opposed the effect on butyrylcholinesterase of 50 to 1, as reported by Thomsen,. . .

SUMM As indicated above, the amount of **galanthamine** is preferably adjusted individually based upon observation of the effect of initially very low dosages. There is as considerable able difference with respect to how sensitive individuals are to acetylcholinesterase inhibitors. Thus, the amount of **galanthamine** is suitably adjusted by means of a regimen starting at low dosages, e.g. 1 mg, preferably at 5 mg, per. . .

SUMM While **galanthamine** has, indeed, given remarkable results, such as appears from the clinical cases given in the examples, it is justified to presume that other acetylcholinesterase inhibitors which are functional equivalents to **galanthamine** with respect to its combination of high selectivity with respect to nicotinic receptor sites and capability of passing the blood. . . a useful combination of effect against fatigue syndrome and acceptability in the clinic, although it cannot be ruled out that **galanthamine**, **galanthamine** salts and **galanthamine** derivatives, due to the special conformation of the **galanthamine** ring system, have specific properties which are decisive for the remarkable effect.

SUMM In accordance with the above, compounds which are functional equivalents of **galanthamine** are defined herein as compounds which

SUMM . . . humans. Both of these tests give further indication of whether the candidate drug has a spectrum of properties equivalent to **galanthamine** with respect to what must be presumed to be essential properties. Peripheral side effects will be assessable when the effect. . . and especially the well-defined in vitro character of the initial screening, the test series for identifying useful functional

equivalents of **galanthamine** is a reasonable an not burdensome routine which is within the realm of the person skilled in the art.

SUMM Functional equivalents and derivatives of **galanthamine** which are useful in the method of the invention will be employed in the same manner as stated herein for **galanthamine**. Whenever quantities of such a functional equivalent or derivative are referred to herein, the quantities are given as the equipotent quantity of **galanthamine** hydrobromide with respect to inhibition of acetylcholinesterase, that is, as the quantity of **galanthamine** hydrobromide which results in the same inhibition of acetylcholine esterase in the above-mentioned in vitro test according to Thomsen et. . .

SUMM . . . in vivo tests as described by Thomsen and Kewitz in the above mentioned paper Selective Inhibition of Human Acetylcholinesterase by **Galanthamine** in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and T. Thomsen, H. Kewitz and O. Pleul, . . . 40-fold) reference to selectivity for acetylcholinesterase as opposed to

butyrylcholinesterase is made in the claims. According to Thomsen and Kewitz, **galanthamine** hydrobromide, when tested under the conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fixpoint" whenever. . . purpose of determining

the selectivities for other cholinesterase inhibitors, as a calibration value which is the one to establish with **galanthamine** hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference to this determination method, a. . .

SUMM . . . as an additional characterization, optionally be expressed with

reference to the in vivo determinations performed by Thomsen and Kewitz on **galanthamine** and described in the above-mentioned paper Selective Inhibition of Human Acetylcholinesterase by **Galanthamine** in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990). With reference to this determination, a preferred acetylcholinesterase. . . in inhibition of at least 50% of the acetylcholinesterase activity in erythrocytes from the adult within about 2-5 minutes. For **galanthamine**, Thomsen and Kewitz found 65% inhibition of acetylcholinesterase in the erythrocytes within 2 minutes after administration of 10 mg of **galanthamine** i.v. in a healthy volunteer, whereas no inhibition of butyrylcholinesterase in plasma was seen. Also these determinations are referred to in claims herein and should, in connection with the evaluation of the corresponding selectivities of candidate drugs different from **galanthamine** hydrobromide be considered the "calibration fixpoints" which will be established with **galanthamine** hydrobromide in any repetition of this experiment.

SUMM As mentioned above, it is possible that **galanthamine**, **galanthamine** salts and **galanthamine** derivatives, due to the special conformation of the **galanthamine** ring system, have specific properties which are decisive for the remarkable effect established according to the present invention. Thus, according. . . and useful in the treatment according to the invention are the compounds

having the formula I (formula I also represent **galanthamine** itself) ##STR1## wherein R.sup.1 and R.sup.2 which may be the same or different each represents a hydrogen atom or an. . .

SUMM A broader range of compounds which, from the point of view of structural

similarity with **galanthamine**, are contemplated to be valuable compounds useful in the method of the invention are **galanthamine**

derivatives of the general formula II ##STR2## wherein the broken line represents an optionally present double bond in one or. . .

SUMM **Galanthamine**, **galanthamine** salts, **galanthamine** derivatives and **galanthamine** functional equivalents, when suited therefor, may be administered orally at a dosage of e.g. 5-150 mg per day, such as. . . often be started with a low dosage and then increased until the suitable dosage has been established. The dosage of **galanthamine** functional equivalents or **galanthamine** derivatives is expressed as the equipotent amount of **galanthamine** hydrobromide, the reference basis being the capability of inhibiting acetylcholinesterase in the Thomsen et al. in vitro test mentioned above.

SUMM For the oral administration, **galanthamine** or a **galanthamine** salt or derivative or a functional equivalent may be formulated, for example, as an aqueous suspension or a solution in. . . are typically of a concentration of 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 10-40 mg/ml, typically 20-30 mg/ml of **galanthamine**. Divided doses into the range 0.5-5 mg/kg body weight per day are useful, in some situations divided doses in the. . .

SUMM **Galanthamine** and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable. . . mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, such as 10-30 mg/ml, especially 20-30 mg/ml of **galanthamine**. As mentioned above, typical dosage rates when administering **galanthamine** by injection are the range 0.01-20 mg per day depending upon the patient. For example, divided doses in the range. . .

SUMM **Galanthamine** and its pharmaceutically acceptable acid addition salts, and its derivatives and functional equivalents, when suited therefor, may be administered by. . .

SUMM The parenteral dosage rate of **galanthamine** can also be expressed by reference to the body weight of the patient; in this case, a normal dosage rate. . .

SUMM . . . techniques may be employed. If desired, a pharmaceutically acceptable carrier such as starch or lactose may be used in preparing **galanthamine** or **galanthamine** equivalent tablets. Capsules may be prepared using soft gelatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of **galanthamine** or functional equivalents thereof which release the contents over a period of several hours thereby maintaining a constant level of **galanthamine** or its functional equivalent in the patient's blood.

SUMM Tablets or capsules containing 0.1, 1, 2, 5, 10 and 25 mg **galanthamine** hydrobromide or functional equivalent to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

SUMM Other interesting administration forms of **galanthamine** and functional equivalents are suppositories, a slow-release plaster, and other depot compositions.

SUMM Although **galanthamine** must be considered as having a high degree of safety, there have been certain side effects in a few of. . .

SUMM The administration forms for the cholinesterase inhibitors, **galanthamine**, the **galanthamine** salts and the **galanthamine** derivatives may be orally and parenterally. The

administration being dependent on the patient's age and weight, and on the daily. . .

DETD . . . the following, it is illustrated how the kit is used for the determination of the activity and selectivity of Nivalin (**Galanthamine** hydrobromide).

DETD The results show a significant reduction of the hemolysate cholinesterase activity with increased concentration of **galanthamine** hydrobromide, whereas the data for the serum activity do not show any statistically significant change as a response to the addition of the **galanthamine** hydrobromide, which is an indication of a high selectivity of the **galanthamine** hydrobromide with respect to acetylcholinesterase as opposed to butyrylcholinesterase. Selectivity for acetylcholinesterase in erythrocytes opposed to butyrylcholinesterase is contemplated to. . .

DETD Formulations of Tablets Containing **Galanthamine**

DETD

Composition of 1 tablet containing 1 mg **galanthamine**

Galanthamine hydrobromide	0.001	g
Calcium phosphate	0.032	g
Lactose	0.005	g
Wheat Starch	0.0056	g
Microcrystalline Cellulose	0.015	g
Talc	0.0007	g
Magnesium Stearate	0.0007	g

Composition of 1 tablet containing 5 mg **galanthamine**

Galanthamine hydrobromide	0.005	g
Calcium phosphate	0.024	g
Lactose	0.004	g
Wheat Starch	0.004	g
Microcrystalline Cellulose	0.04	g
Talc	0.002	g
Magnesium Stearate	0.001	g

Composition of 1 tablet containing 10 mg **galanthamine**

Galanthamine hydrobromide	0.010	g
Lactose	0.040	g
Wheat Starch	0.0234	g
Microcrystalline Cellulose	0.0374	g
Talc	0.0036	g
Magnesium Stearate	0.0012	g
Gelatin	0.0044	g

DETD 11 of the persons were randomly allocated to **galanthamine** treatment, and the remaining 9 to placebo treatment. The protocol for the trial made provisions for the clinician to opt. . .

DETD In order to assess any underlying, overall performance difference between the **galanthamine** and placebo treated patients, the median (the statistic which differentiates the upper and lower 50% of scores) of the changes. . .

DETD Using this median as an index of average "placebo response", it was found that 68.18% of **galanthamine** treated patients changes on the analogue scales fall above the placebo median, a difference (from the top 50% of placebo treated patients) which is statistically significant (exact p=0.033). This demonstrates an underlying trend for CFS patients treated with **galanthamine** to generate more

beneficial changes on these visual analogue scales, which cannot be explained as a `placebo response`.

DETD . . . it was found that at this point all 9 of the patients randomly allocated to the placebo were transferred to **galanthamine**, whilst only 1 of the 11 patients receiving **galanthamine** was transferred to placebo treatment. Such a difference (i.e. 9/9 vs 1/11) is highly significant (exact p=0.00006). It is worth noting that the one patient transferred from **galanthamine** to placebo, after 2 weeks on placebo was found to have failed to respond and was returned to **galanthamine**.

DETD TABLE 6.1

MEANS (STANDARD ERRORS) OF VISUAL ANALOGUE SCALES

Scale	Treatment (N)	Baseline	After 1 Week	After 2 Weeks
Sleep	**Galanthamine** (11)	20.78	17.90	18.42
		(2.13)	(2.25)	(2.09)
Disturbance	Placebo (9)	22.96	19.51	18.22
		(1.34)	(2.44)	(2.96)
Fatigue	**Galanthamine** (11)	29.41	29.76	25.21
		(1.64)	(1.70)	(2.32)
	Placebo (9)	28.52	27.67	26.53
		(1.97)	(2.26)	(1.77)
Myalgia	**Galanthamine** (11)	17.58	15.95	13.58
		(0.74)	(0.73)	(1.26)
	Placebo (9)	17.26		

(0.71)
16.03
(1.02)
14.69
(0.95)

Work **Galanthamine** (11)
9.43
(1.17)
11.61
(1.28)
9.64
(1.61)

Capacity/
Placebo (9)
11.29
(0.99)
10.80
(1.36)
9.43
(1.21)

Satisfaction
Memory Galanthamine (11)
5.31
(0.93)
5.89
(0.90)
5.62
(0.90)

Placebo (9)
6.64
(0.75)
5.66
(0.81)
5.02
(0.81)

Dizziness
Galanthamine (11)
9.05
(1.26)
9.00
(1.79)
8.79
(1.81)

Placebo (9)
6.47
(1.61)
6.94
(1.78)
7.52
(2.01)

DETD The changes on the visual analogue scales of all **galanthamine** treated patients during treatment has been assessed, both those patients randomly allocated to **galanthamine** and those transferred from placebo, during the total eight weeks of the trial. These data are presented in Table 6.2.

DETD TABLE 6.2

MEANS (STANDARD ERRORS) OF **GALANTHAMINE** TREATED

PATIENTS ON VISUAL ANALOGUE SCALES

Scale	Baseline	1 Week	2 Weeks	4 Weeks	8 Weeks
	N = 19	N = 19.	.	.	(2.21)
Myalgia	16.32	(0.69)	14.25	(0.89)	11.24
				(1.12)	12.01
					(1.15)
					10.51
					(0.98)
Work	9.21	(0.83)	10.22	(1.07)	8.21
					(1.17)
					7.40
					(1.25)
					7.34
					(1.12)
Memory	5.10	(0.64)	5.41	(0.61)	4.79
					(0.59)
					4.33
					(0.70)
					4.50
					(0.68)
Dizziness	8.39	(1.18)	8.96	(1.40)	6.94
					(1.40)
					6.30
					(1.32)
					4.77
					(1.23)

DETD Data from the Cognitive Failures Questionnaire are available for all **galanthamine** treated patients at baseline and after 6 and 8 weeks of treatment. These are presented in Table 6.4:

DETD The present data appear to provide clear and consistent evidence in favour of the therapeutic efficacy of **galanthamine** in the treatment of CFS. This evidence is derived from an interpretation of the patients' overall self-evaluation of the beneficial. . . treatment after only two weeks of treatment, and made a comparable switch to

placebo treatment in only one patient receiving **galanthamine**. Additional evidence of the beneficial effects of **galanthamine** comes form the observed significant improvements on a visual search task

(a well validated test of concentration and **attention**), and similar improvements on a questionnaire designed to evaluate **cognitive** failures.

DETD Tablet containing 10 mg **galanthamine**

DETD From the results in the depressed person it is seen that the potentials change after treatment with **galanthamine**, such as explained above. This means that **galanthamine** must be able to cross the blood-brain barrier, since it is possible to inhibit in synapsis in the brain stem,. . .

DETD . . . shows the auditory evoked response of a depressed patient (a manio depressed patient in the depressed state) without treatment with **galanthamine**.

DETD . . . evoked response of a depressed patient (the same as in FIG. 1A)

2 hours after treatment with 10 mg of **galanthamine**.

DETD FIG. 2A shows the auditory evoked response of a healthy person without treatment with **galanthamine**.

DETD . . . evoked response of a healthy person (the same as in FIG. 2A) 2 hours after treatment with 10 mg of **galanthamine**.

CLM What is claimed is:

8. A method according to claim 1, wherein the cholinesterase inhibitor is selected from the group consisting of **galanthamine** and **galanthamine** derivatives, norgalanthamine and norgalanthamine derivatives, epigalanthamine and epigalanthamine derivatives, physostigmine, tacrine and tacrine analogues, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, and. . .

17. A method according to claim 1, in which the cholinesterase inhibitor is **galanthamine** or a salt, derivative or functional equivalent thereof.

. . . for the treatment of a fatigue syndrome, comprising administering, to a patient in need thereof, an effective amount of a **galanthamine** or a **galanthamine** salt or a **galanthamine** derivative.

20. A method according to claim 19, in which the compound is a **galanthamine** derivative of the general formula II ##STR4## wherein the broken line represents an optionally present double bond in one or. . .

21. A method according to claim 19, in which the compound is **galanthamine** or a derivative of **galanthamine** and has the formula I ##STR5## wherein R.sup.1 and R.sup.2 which may be the same or different each represents a. . .

22. A method according to claim 19, wherein the **galanthamine** salt is **galanthamine** hydrobromide.

29. A method according to claim 19, wherein the **galanthamine** derivative is one which is able to cross the blood brain barrier in humans.

30. A method according to claim 19, wherein the cholinesterase inhibitor or the **galanthamine** or the **galanthamine** salt or the **galanthamine** derivative is administered in the form of a

pharmaceutical composition which is a tablet, a capsule, a sustained release capsule. . .
31. A method according to claim 19, in which the cholinesterase inhibitor or the **galanthamine** or the **galanthamine** salt or the **galanthamine** derivative is administered parenterally at a dosage which is equipotent with 0.1-1,000 mg of **galanthamine** hydrobromide per day, such as 5-1,000 mg of **galanthamine** hydrobromide.

. . . to claim 31, in which the cholinesterase inhibitor is administered in a dosage which is equipotent with to 10-500 mg **galanthamine** hydrobromide per day, such as 50-300 mg per day.

. . . 32, in which the cholinesterase inhibitor is administered in a dosage which is equipotent with 10-50, in particular 10-30, mg **galanthamine** hydrobromide per day.

. . . to claim 1, in which the cholinesterase inhibitor is administered orally in a dosage which is equipotent with 5-2000 mg **galanthamine** hydrobromide per day.

. . . according to claim 33, in which the cholinesterase inhibitor is administered at a dosage which is equipotent with 10-500 mg **galanthamine** hydrobromide per day.

. . . which the cholinesterase inhibitor is administered at a dosage which is equipotent with 10-50 mg, such as 10-30 mg, of **galanthamine** hydrobromide per day.

IT 52-68-6 57-47-6 321-64-2 321-64-2D, analogs **357-70-0**, Galanthamine 1668-85-5 16088-19-0 41303-74-6 51581-32-9 86697-68-9, Fasciculin 101246-68-8 102518-79-6
(benzodiazepines hypnotic and sedative activity inhibition by, in humans)

=> s LDL or low density lipoprotein
L16 172504 LDL OR LOW DENSITY LIPOPROTEIN

=> s galanthamine or lycoramine or 21133-52-8/rn or 357-70-0/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L17 2237 GALANTHAMINE OR LYCORAMINE OR 21133-52-8/RN OR 357-70-0/RN

=> s l16 and l17
L18 3 L16 AND L17

=> d l18 1-3 ab bib kwic

L18 ANSWER 1 OF 3 USPATFULL
AB Methods of preventing, treating, or ameliorating symptoms of Alzheimer's Disease, regulating production or levels of amyloid .beta. (A.beta.) peptides and/or regulating the amount of ApoE isoform 4 in the bloodstream and/or brain are provided which include the step of administering to a subject in need of such treatment an effective amount

of a composition including at least one compound represented by Formulae
(I-X) disclosed herein.
AN 2003:17945 USPATFULL
TI Methods for treating alzheimer's disease and/or regulating levels of amyloid beta peptides in a subject
IN Davis, Harry R., Bekeley Heights, NJ, UNITED STATES
Parker, Eric McFee, Scotch Plains, NJ, UNITED STATES
van Heek, Margaret, Scotch Plains, NJ, UNITED STATES
Wong, Gwendolyn T., Westfield, NJ, UNITED STATES
Merkel, Laura B., Princeton, NJ, UNITED STATES
PI US 2003013699 A1 20030116
AI US 2002-154106 A1 20020522 (10)
PRAI US 2001-323911P 20010921 (60)
US 2001-293651P 20010525 (60).
DT Utility
FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 64
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4690
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . Pfizer), rivastigmine tartrate (such as EXELON which is available from Novartis), tacrine (such as COGNEX which is available from Parke-Davis), **galanthamine** derivatives available from Janssen, metrifonate available from Bayer Corp., ipidacrine available from Nikken Chemicals Co. Ltd., TAK-147, T-82 available from. . .
SUMM [0591] PPAR.alpha. activator compounds are useful for, among other things, lowering triglycerides, moderately lowering **LDL** levels and increasing HDL levels. Useful examples of PPAR.alpha. activators include fibrates.
SUMM . . . of their non-systemic mode of action. Bile acid sequestrants can lower intrahepatic cholesterol and promote the synthesis of apo B/E (**LDL**) receptors which bind **LDL** from plasma to further reduce cholesterol levels in the blood.
SUMM . . . in combination with the compound(s) of Formulae I-X discussed above. The IBAT inhibitors can inhibit bile acid transport to reduce **LDL** cholesterol levels. Non-limiting examples of suitable IBAT inhibitors include benzothiepines such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such. . .
SUMM . . . nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide). Nicotinic acid and its derivatives inhibit hepatic production of VLDL and its metabolite **LDL** and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN.RTM. (niacin extended-release tablets). . .
SUMM . . . in the methods of the present invention can further comprise one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can reduce **LDL** and VLDL levels, coadministered with or in combination with the compound(s) of Formulae I-X discussed above. ACAT is an enzyme. . .
SUMM . . . or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Pat. Nos. 6,121,319 and 6,147,250), which can reduce **LDL** and HDL levels, coadministered with or in combination with the compound(s) of Formula I-X discussed above.
SUMM . . . In another alternative embodiment, the compositions used in the
methods of the present invention can further comprise one or more

low-density lipoprotein (LDL)
receptor activators, coadministered with or in combination with the compound(s) of Formulae I-X discussed above. Non-limiting examples of suitable **LDL**-receptor activators include HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates **LDL** receptor activity. See M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the **LDL** Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12.

SUMM [0617] Generally, a total daily dosage of **LDL** receptor activator(s) can range from about 1 to about 1000 mg/day in single or 2-4 divided doses.

SUMM . . . preferably less than about 180 and can range from about 150 to about 200 mg/dl. In another embodiment, the total **LDL** cholesterol level is less than about 100 mg/dl, more preferably less than about 90 mg/dl and can range from about 30 to about 100 mg/dl. Methods of measuring serum total blood cholesterol and total **LDL** cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498. . .

SUMM . . . and can range from about 200 to about 1000 mg/dl. In another alternative embodiment, the subject has an elevated total **LDL** cholesterol level. In another embodiment, the total **LDL** cholesterol level is greater than about 100 mg/dl, more preferably greater than about 110 mg/dl and can range from about. . .

CLM What is claimed is:
22. The method according to claim 1, wherein the total **LDL** cholesterol level of the subject is greater than about 100 mg/dl.

37. The method according to claim 1, wherein the composition further comprises at least one **low-density lipoprotein** receptor activator.

L18 ANSWER 2 OF 3 USPATFULL

AB The present invention provides methods and compositions for screening, diagnosis and prognosis of Alzheimer's disease, for monitoring the effectiveness of Alzheimer's disease treatment, and for drug development. Alzheimer's Disease-Associated Features (AFs), detectable by two-dimensional electrophoresis of cerebrospinal fluid, serum or plasma are described. The invention further provides Alzheimer's Disease-Associated Protein Isoforms (APIs) detectable in cerebrospinal fluid, serum or plasma, preparations comprising isolated APIs, antibodies, pharmaceutical compositions, diagnostic and therapeutic methods, and kits comprising or based on the same.

AN 2002:294625 USPATFULL

TI Nucleic acid molecules, polypeptides and uses therefor, including diagnosis and treatment of alzheimer's disease

IN Durham, L. Kathryn, New London, CT, UNITED STATES
Friedman, David L., Madison, CT, UNITED STATES
Chandrasiri Herath, Herath Mudiyanselage Athula, Abingdom, UNITED KINGDOM
Kimmel, Lida H., Chester, CT, UNITED STATES
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PI US 2002164668 A1 20021107
AI US 2001-826290 A1 20010403 (9)
PRAI US 2000-194504P 20000403 (60)
US 2000-253647P 20001128 (60)
DT Utility
FS APPLICATION
LREP KLAUBER & JACKSON, 411 Hackensack Avenue, Hackensack, NJ, 07601
CLMN Number of Claims: 50
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 5696
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . Chicken ACCURATE CHEMICAL &
IMS-01-026-02
anti- SCIENTIFIC CORPORATION
API-34 Cystatin C, Rabbit anti-Human ACCURATE CHEMICAL &
AXL-574
SCIENTIFIC CORPORATION
API-37 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-38 C4 Complement, Chicken ACCURATE CHEMICAL &
IMS-01-032-02
. . . RDI RESEARCH DIAGNOSTICS, RDI-
INC
CLUSTRCabG
API-47 ANTI-Human CD56 ANTIGEN RDI RESEARCH DIAGNOSTICS,
RDI-CBL159
(NEURAL CELL ADHESION INC
MOLECULE)
API-50 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-52 Alpha-1-Antichymotrypsin, ACCURATE CHEMICAL &
AXL-145/2
Rabbit anti-Human. . . (NEURAL CELL ADHESION INC
MOLECULE)
API-60 Gelsolin, plasma + ACCURATE CHEMICAL &
YBG-4628-6210
cytoplasmic, Sheep anti- SCIENTIFIC CORPORATION
API-62 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-64 C4 Complement, Chicken ACCURATE CHEMICAL &
IMS-01-032-02
anti-Human SCIENTIFIC CORPORATION
API-66 Retinol Binding Protein, ACCURATE CHEMICAL &
AXL-163/2
Rabbit anti-Human SCIENTIFIC CORPORATION
API-67 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-69 Complement Factor B, C3 ACCURATE CHEMICAL &. . .
(B.beta. 1-42), Clone: 18C6, SCIENTIFIC CORPORATION
Mab anti-Human
API-76 C3 Complement, Chicken ACCURATE CHEMICAL &

IMS-01-001-02
anti-Human SCIENTIFIC CORPORATION
API-77 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-78 C3 Complement, Chicken ACCURATE CHEMICAL &
IMS-01-001-02
. . . CORPORATION
API-103 Goat anti-Haptoglobin BIODESIGN INTERNATIONAL
L15320G
API-104 Transthyretin, Prealbuminm, ACCURATE CHEMICAL &
MED-CLA 193
55kD, Rabbit anti-Human SCIENTIFIC CORPORATION
API-113 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-118 Monoclonal anti-human BIODESIGN INTERNATIONAL
N77190M
Fibrinogen
API-119 Monoclonal. . . Goat anti-Clusterin (human) RDI
RESEARCH DIAGNOSTICS, RDI-
INC
CLUSTRCabG
API-136 Goat anti-Clusterin (human) RDI RESEARCH DIAGNOSTICS,
RDI-
INC
CLUSTRCabG
API-137 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-138 C4 Complement, Chicken ACCURATE CHEMICAL &
IMS-01-032-02
. . . Complement, Chicken ACCURATE CHEMICAL &
IMS-01-032-02
anti-Human SCIENTIFIC CORPORATION
API-170 Goat anti-Clusterin (human) RDI RESEARCH DIAGNOSTICS,
RDI-
INC
CLUSTRCabG
API-171 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-172 C4 Complement, Chicken ACCURATE CHEMICAL &
IMS-01-032-02
. . . RDI RESEARCH DIAGNOSTICS, RDI-
INC
CLUSTRCabG
API-175 Transthyretin, Prealbuminm, ACCURATE CHEMICAL &
MED-CLA 193
55kD, Rabbit anti-Human SCIENTIFIC CORPORATION
API-176 Apolipoprotein E, **LDL**, VLDL, ACCURATE CHEMICAL &
YM-5029
Clone: 3D12, Mab anti- SCIENTIFIC CORPORATION
Human, frozen/paraffin
API-178 Transthyretin, Prealbuminm, ACCURATE CHEMICAL &
MED-CLA 193

. . .	Rabbit anti-Human	ACCURATE CHEMICAL & SCIENTIFIC CORPORATION	AXL-574
API-220	C4 Complement, Chicken IMS-01-032-02 anti-Human	ACCURATE CHEMICAL & SCIENTIFIC CORPORATION	
API-221	Apolipoprotein E, **LDL**, VLDL, YM-5029 Clone: 3D12, Mab anti-Human, frozen/paraffin	ACCURATE CHEMICAL & SCIENTIFIC CORPORATION	
API-223	C4 Complement, Chicken IMS-01-032-02 anti-Human	ACCURATE CHEMICAL & SCIENTIFIC CORPORATION	
API-225	Apolipoprotein E, **LDL**, VLDL, YM-5029 Clone: 3D12, Mab anti-Human, frozen/paraffin	ACCURATE CHEMICAL & SCIENTIFIC CORPORATION	
API-233	Apolipoprotein E, **LDL**, VLDL, YM-5029 Clone: 3D12, Mab anti-Human, frozen/paraffin	ACCURATE CHEMICAL & SCIENTIFIC CORPORATION	
API-238	Apolipoprotein D, Clone: MED-CLA457	ACCURATE CHEMICAL &	

. . .

DETD . . . therapy, physostigmine, rivastigmine, hepastigmine, metrifonate, ENA-713, ginkgo biloba extract, physostigmine, amridin, talsaclidine, zifrosilone, eptastigmine, methanesulfonyl chloride, nefiracetam, ALCAR, talsachidine, xanomeline, **galanthamine**, and propentofylline.

L18 ANSWER 3 OF 3 USPATFULL

AB Therapeutic compositions comprising an effective amount of at least one carbonyl trapping agent alone or in combination with a therapeutically effective of a co-agent or medicament are disclosed. The compositions are used to treat a mammal suffering from a neurological disease characterized by covalent bond crosslinking between the nerve cells, other cellular structures and their intracellular and extracellular components, with disease induced carbonyl-containing aliphatic or aromatic hydrocarbons present in mammals.

AN 97:83944 USPATFULL

TI Methods of treating neurological diseases and etiologically related symptomology using carbonyl trapping agents in combination with previously known medicaments

IN Shapiro, Howard K., 214 Price Ave. F32, Narberth, PA, United States 19072

PI US 5668117 19970916

AI US 1993-62201 19930629 (8)

RLI Continuation-in-part of Ser. No. US 1993-26617, filed on 23 Feb 1993, now abandoned which is a continuation of Ser. No. US 1991-660561, filed on 22 Feb 1991, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Kight, John; Assistant Examiner: Leary, Louise

LREP Perrella, D. J.

CLMN Number of Claims: 29

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 3963

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and coworkers, 1988; Davies, 1991, pg. S-25), metrifonate (Becker and Giacobini, 1988), velnacrine maleate (Cooper, 1991; Cutler

and coworkers, 1992), **galanthamine** (Nivalin) (Ferris, 1990; Sweeney and coworkers, 1990), sulfonyl fluorides such as methanesulfonyl
. fluoride (Moos and Hershenson, 1989) and phenylmethylsulfonyl fluoride.
. .
SUMM . . . and Padilla, 1990), huperzine A (Moos and Hershenson, 1989), huperzine B (Tang and coworkers, 1989), edrophonium (Flood and coworkers, 1988), **galanthamine** (Nivalin) (Sweeney and coworkers, 1990), metrifonate (Moos and Hershenson, 1989) and velnacrine
(Cutler and coworkers, 1992); (c) cholinergic muscarinic agonists. .
.
SUMM . . . (b) cisapride (Prepulsid) (Bergmann and coworkers, 1992); (c) famotidine (Pepcid); (d) cimetidine (Tagamet); (e) ranitidine (Zantac); (f) omeprazole (Prilosec); and **galanthamine** (Sweeney and coworkers, 1990).
SUMM . . . products in the etiology of atherosclerosis (Halliwell, 1991, pg. 583). 4-Hydroxy-2,3-transnonenal covalently binds to lysine and other peptide residues of **low-density lipoprotein** much more readily than malondialdehyde. Hence, it (as well as other aldehydes) may play a role in the etiology of. . . there is reason to believe that reactive lipid peroxidation agents form Schiff base adducts with the lysine epsilon-amino groups of **low density lipoproteins** (**LDL**). Such modified **LDL**'s are recognized by high-affinity acetyl-**LDL** receptors located on macrophages, which results in lipid accumulation. Lipid-laden macrophages appear to be precursors of the foam cells which.
. .
DETD **galanthamine**, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily; and
DETD **galanthamine**, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily; and
DETD (g) **galanthamine**, intravenous, intramuscular, subcutaneous or oral dosage range from 5 mg daily to 100 mg daily.
DETD Esterbauer, H. et al. "Autoxidation of human **low density lipoprotein**: Loss of polyunsaturated fatty acids and vitamin E and generation of aldehydes" J. Lipid Res. 28:495-509 (1987)
DETD Jurgens, G. et al. "Modification of human **low-density lipoprotein** by the lipid peroxidation product 4-hydroxynonenal" Biochim. Biophys. Acta 875:103-114 (1986)
DETD Steinbrecher, U. P. "Oxidation of human **low density lipoprotein** results in derivatization of lysine residues of apolipoprotein B by lipid peroxide decomposition products" J. Biol. Chem. 262:3603-3608 (1987)
DETD Sweeney, J. E. et al. "Effects of different doses of **galanthamine**, a long-acting acetylcholinesterase inhibitor, on memory in mice" Psychopharmacology 102:191-200 (1990)
CLM What is claimed is:
. . . least one of the following medications: (a) metoclopramide; (b) cisapride; (c) famotidine; (d) cimetidine; (e) ranitidine; (f) omeprazole; and (g) **galanthamine**, wherein the composition is adapted to administer both the carbonyl trapping primary amine and the medicament via the same route.
. . .
IT 50-18-0, Cyclophosphamide 54-96-6, 3,4-Diaminopyridine 56-40-6, Glycine, biological studies 57-47-6, Physostigmine 58-56-0, Pyridoxine hydrochloride 58-85-5, Biotin 59-02-9 59-30-3, Folic acid, biological studies 59-43-8, Thiamine, biological studies

59-51-8, D,L-Methionine 59-67-6, Nicotinic acid, biological studies 59-92-7, Levodopa, biological studies 68-19-9, Vitamin B12 68-41-7, D-Cycloserine 72-19-5, L-Threonine, biological studies 79-83-4, Pantothenic acid 83-88-5, Vitamin B2, biological studies 98-92-0, Nicotinamide 137-08-6 137-58-6, Lidocaine 150-13-0, p-Aminobenzoic acid 302-79-4D, Retinoic acid, derivs. 302-84-1, Serine 321-64-2, Tacrine **357-70-0**, Galanthamine 364-62-5, Metoclopramide 446-86-6, Azathioprine 456-59-7, Cyclandelate 504-24-5, 4-Aminopyridine 645-88-5, Aminooxyacetic acid 657-24-9, Metformin 768-94-5, Amantadine 1134-47-0, Baclofen 1195-16-0 1406-18-4, Vitamin E 3200-06-4, Praxilene 3286-46-2, Sulbutiamine 4759-48-2, 13-cis-Retinoic acid 7235-40-7, .beta.-Carotene 7491-74-9, Piracetam 7782-49-2, Selenium, biological studies 8059-24-3, Vitamin B6 9004-10-8D, Insulin, derivs., biological studies 11000-17-2D, Vasopressin, analogs 13345-51-2D, Prostaglandin B1, oligomers 14611-51-9, Selegiline 15301-69-6, Flavoxate 18601-90-6, Thiamine mononitrate 23210-56-2, Ifenprodil 24305-27-9, Thyrotropin releasing factor 28704-27-0 28860-95-9, Carbidopa 37758-47-7, Ganglioside GM1

41708-72-9, Tocainide 51012-32-9, Tiapride 51037-30-0, Acipimox 51481-61-9, Cimetidine 54143-55-4, Flecainide 59865-13-3, Cyclosporine 66357-35-5, Ranitidine 72432-10-1, Aniracetam 73590-58-6, Omeprazole 76824-35-6, Famotidine 81098-60-4, Cisapride 103878-84-8, Lazabemide 105431-72-9, Linopirdine 196966-12-8, Anfacine

(carbonyl trapping agent combination with other drug for treatment of neurol. diseases and etiol. related symptomol.)

=>

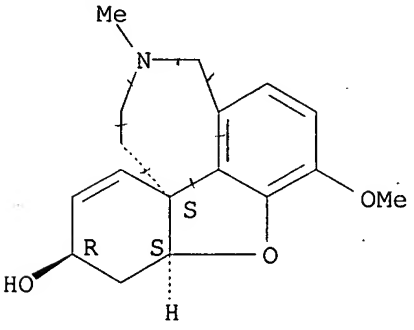
5/4/215 nicotine 514/343

L2 1 GALANTHAMINE/CN

=> d

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 357-70-0 REGISTRY
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl- (7CI)
CN **Galanthamine (6CI, 8CI)**
OTHER NAMES:
CN (-)-Galanthamine
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, [4aS-(4a.alpha.,6.beta.,8aR*)]-
CN Galantamin
CN Galantamine
CN Jilkon
CN Lycoremin
CN Lycoremine
CN [4aS-(4a.alpha.,6.beta.,8aR*)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol
FS STEREOSEARCH
DR 736-79-8, 1551-02-6
MF C17 H21 N O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HODOC*, IPA, MEDLINE, MRCK*, NAPRALERT, PHAR, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry. Rotation (-).



Cholinesterase inhibitors:
Ecothiophate 514/75
Edrophonium 514/700
Neostigmine 514/555

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

602 REFERENCES IN FILE CA (1957 TO DATE)
21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
603 REFERENCES IN FILE CAPLUS (1957 TO DATE)
27 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> s lycoramine
L3          43 LYCORAMINE

=> s lycoramine/cn
L4           1 LYCORAMINE/CN

=> d

L4   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   21133-52-8  REGISTRY
CN   6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol,
4a,5,7,8,9,10,11,12-octahydro-3-
     methoxy-11-methyl-, (4aS,6S,8aS)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Galanthamine, 1,2-dihydro-
CN   Galanthamine, dihydro- (6CI)
CN   Lycoramine (7CI, 8CI)
OTHER NAMES:
CN   1,2-Dihydrogalanthamine
CN   Dihydrogalanthamine
DR   468-48-4, 1359-29-1
MF   C17 H23 N O3
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA,
       CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, EMBASE, MRCK*,
       NAPRALERT, SPECINFO, TOXCENTER, USPATFULL
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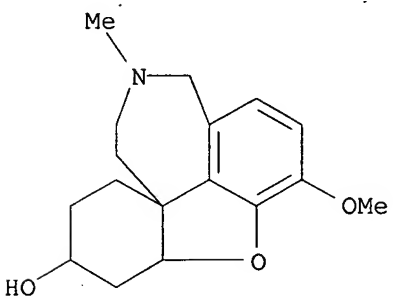


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             60 REFERENCES IN FILE CA (1957 TO DATE)
              5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             61 REFERENCES IN FILE CAPLUS (1957 TO DATE)
              8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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